FROM PSYCHOSIS TO AFFECTIVE DISORDER:

PSYCHEDELICS AS PHARMACOLOGICAL MODELS FOR PSYCHIATRIC RESEARCH

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Summary

Recent studies into the molecular, pharmacological and behavioral basis of psychotomimetics such as the glutamate N-methyl- D -aspartate receptor (NMDAR) antagonist ketamine and the mixed 5-hydroxytryptamine (5-HT) receptor agonist psilocybin in healthy human subjects suggest that both the glutamatergic and serotonergic system are implicated in the pathophysiolology of psychotic disorders such as schizophrenia. Specifically, administration of ketamine to healthy humans reproduces positive and negative symptoms as well as cognitive impairments that are seen in acute and chronic schizophrenia, while the mixed 5-HT2A/1A receptor agonist psilocybin engenders positive symptoms and cognitive deficits that resemble the symptoms seen in incipient or acute phases of schizophrenia. Moreover, the observation that both ketamine and psilocybin also disrupt sensory gating (e.g. PPI, P50) in healthy subjects comparable to that seen in schizophrenia has led to the widespread use of these drugs to provide models for identifying neurobiological factors that are crucial to the pathophysiology of schizophrenia and to the development of novel treatments. Along this line, it has repeatedly been demonstrated that schizophrenia patients also show a reduced mismatch-negativity (MMN) event-related potential (ERP). The MMN is interpreted as a prediction error signal during implicit perceptual learning. The processing of prediction errors is of considerable importance in regard to psychosis, because recent theories posit that aberrant encoding of prediction errors may underlie the expression of psychotic symptoms. Furthermore, the MMN (i.e. prediction error processing) depends critically on NMDAR-dependent synaptic plasticity. In fact ketamine disrupts MMN responses in healthy humans comparable to those observed in schizophrenia. Given that neuromodulatory transmitters like 5-HT are thought to be implicated in the regulation of NMDAR-dependent synaptic plasticity during prediction error processing, it is conceivable that psilocybin may also, though via a differential mechanism, affect the MMN expression in humans.

Based on this background, we investigated in the present thesis *(chapter 2)* whether the encoding of prediction error (via the assessment of the MMN expression) is affected by S-ketamine or psilocybin and whether the encoding of prediction errors under placebo can be used to predict drug-induced symptoms. In brief, we found that S-ketamine, but not psilocybin, disrupted the processing of prediction errors as expressed by a disrupted MMN expression over fronto-central brain regions. Although both drugs produced positive-like symptoms, we found that only S-ketamine produced severe cognitive impairments, the extent of which significantly correlated with the processing of prediction errors under placebo. Our results suggest that the NMDAR, but not the 5-HT receptor system, is critically implicated in the processing of prediction errors during MMN generation as a form of implicit perceptual learning and that aberrant prediction error signaling contributes to the formation of cognitive impairment in this pharmacological model. Our results provide further insights into the pathophysiology of key cognitive symptoms of psychotic disorders and suggest that the assessment of the MMN expression in schizophrenia may allow detecting early phases of the illness and might also serve to assess the efficacy of novel pharmacological treatments, in particular of cognitive impairments. Moreover, in *chapter 3* of this thesis we used a computational model-based approach to examine whether the known NMDAR-mediated reduction of MMN expression can explain the changes in the plasticity of glutamatergic long-range connections among hierarchically related auditory areas.

In other words, we have conducted a quantitative connectivity analysis to determine the coupling parameters, which significantly distinguished between placebo and S-ketamine conditions and also predicted changes in psychotic symptoms following S-ketamine administration. Summarized, quantitative connectivity analysis using dynamic causal modeling (DCM) revealed a significant reduction in bottom-up effective connectivity following S-ketamine administration. Moreover, this model-based estimate of ketamine effects on synaptic plasticity correlates significantly with subjects' introspective ratings of ketamine-induced impairments in cognition and control. Our findings suggest a concrete mechanism for ketamine effects on MMN expression that correlates with drug-induced psychopathology and demonstrate the potential of model-based approaches for inferring synaptic mechanisms of brain responses, and their pharmacological modulation, from non-invasive EEG data.

Apart from the experimental use of psychotomimetic compounds to model psychosis, previous work in the sixties and more recent studies into the clinical effects of psilocybin and ketamine showed that both compounds reveal mood enhancing properties and an antidepressant potential. Specifically, recent studies reported that acute ketamine administration ameliorates depressive symptoms in treatment- resistant depression within a few hours persisting for several days, while acute psilocybin was reported to enhance mood and reduce anxiety in terminal cancer patients. Imaging studies of ketamine and psilocybin in healthy subjects suggest that both drugs may modulate emotional processing by targeting a prefrontal-limbic-occipital network in a similar way. However, the neuronal basis of the effect of psilocybin and ketamine on emotional processing has not yet been investigated in an operationalized manner. To investigate further the neuronal underpinnings of the effect of psilocybin and S-ketamine on emotional processing, in *chapter 4* of this thesis we examined for the first time whether psilocybin and S-ketamine affect visually evoked ERP responses (i.e. P100 and N170 ERP) to facial expressions in a valence specific manner, and second whether these effects vary as a function of visual awareness. Notably, emotional face processing is fundamental to social interaction and behavior and its critical importance in human social functioning is shown by the fact that emotional faces increase neuronal activity relative to neutral faces in visual face-selective areas of the brain, even in the absence of conscious awareness. Thus, modulation of face-selective responses in the visual cortex by emotional expression might correspond to a fundamental regulatory role of basic emotional signals associated with social appraisal and cognition. Our results revealed that the effects of psilocybin and S-ketamine on the early visual N170 ERP depended on the extent of visual awareness. Furthermore, both psilocybin and S-ketamine reduced early visual N170 ERP response to fearful faces, whereas S-ketamine, but not psilocybin, also reduced the N170 ERP response to happy faces. Our findings suggest that psilocybin and S-ketamine differentially contribute to the modulation of visual responses to emotional facial expressions. The present study shall provide a better understanding of the mood enhancing properties of psilocybin and ketamine and shall also allow us to lay the ground for further investigations on the clinical potential of ketamine and psilocybin to treat symptoms of affective disorders. Along this line, the assessment of early visual responses to emotional expressions may provide a useful framework to detect pharmacologically induced changes in emotional processing and might also lead to a greater understanding of pharmacological mechanisms underlying emotional processing and its dysfunction in affective disorders.

Zusammenfassung

In den vergangen Jahren haben molekulare, pharmakologische und verhaltensbezogene Studien zu den Grundlagen von psychotomimetischen Substanzen bei gesunden Probanden – wie der N-Methyl-D-Aspartat Rezeptor (NMDAR) Antagonisten Ketamin oder der gemischte 5-Hydroxytryptamin (5-HT) Rezeptor Agonist Psilocybin – darauf hingewiesen, dass sowohl das glutamaterge als auch das serotonerge System zur Manifestation schizophrener Psychosen beitragen. Genauer gesagt führt die Verabreichung von Ketamin bei gesunden Probanden vorübergehend zu Positivsymptomen (z.B. Wahn), Negativsymptomen (z.B. Affektverflachung) und kognitiven Störungen, wie sie in der akuten und chronischen Schizophrenie zu beobachten sind. Die Verabreichung von Psilocybin hingegen führt bei Gesunden vor allem zu Positivsymptomen und kognitiven Störungen, die entsprechend und häufig in frühen Phasen der Schizophrenie auftreten. Weiter konnte gezeigt werden, dass Ketamin und Psilocybin zudem die sensorische Filterleistung des Gehirns bei gesunden Probanden reduziert (z.B PPI und P50), was vergleichbar mit dem Defizit bei schizophrenen Patienten ist. Diese Erkenntnis hat zu einer zunehmenden experimentellen Anwendung von psychotomimetischen Substanzen geführt (Modellpsychosen), welche dazu dienen, neurobiologische Korrelate (Grundlagen) schizophrener Psychosen aufzudecken. Des Weiteren konnten zahlreiche Untersuchungen zeigen, dass schizophrene Patienten auch ein Defizit in der Ausprägung des Ereignis-korrelierten Potentials (EKP) der „mismatch negativity“ (MMN) aufweisen. Die MMN ist eine negative EKP Komponente, welche implizit während perzeptuellen Lernprozessen aufgebaut wird und als „prediction error“ (PE) Signal verstanden werden kann. Die einwandfreie Generierung und Verarbeitung des PEs ist hinsichtlich psychotischer Episoden von entscheidender Bedeutung, da theoretische Modelle eine fehlerhafte Verarbeitung des PEs als einen möglichen Mechanismus für die Entstehung psychotischer Symptome postulieren. Des Weiteren wissen wir, dass die MMN Expression (d.h. die Verarbeitung des PEs) von einer NMDAR abhängigen synaptischen Plastizität vermittelt wird. Diesbezüglich ist von Bedeutung, dass Ketamin bei Gesunden die MMN Expression signifikant reduziert, ähnlich wie es bei schizophrenen Patienten zu sehen ist. Da angenommen wird, dass modulierende Neurotransmitter wie 5-HT zudem die NMDAR vermittelte Plastizität während der Verarbeitung des PEs regulieren, ist es denkbar, dass Psilocybin über einen differenzierten Mechanismus die Expression der MMN beeinflussen könnte.

Basierend auf diesem Hintergrund haben wir im *Kapitel 2* dieser Arbeit untersucht, wie die Verarbeitung von PEs (via der Erfassung der MMN Expression) durch die Verabreichung von S-Ketamin und Psiloybin beeinflusst wird. Zudem untersuchten wir, ob die Verarbeitung von PEs unter Placebo, d.h. ohne Substanzeinfluss, prädiktiv für gewisse Substanz induzierte Symptome ist. Unsere Resultate zeigen, dass beide Modellsubstanzen vorübergehend moderate psychotische Symptome auslösen, jedoch nur S-Ketamin ausgeprägte kognitive Defizite induziert. Des Weiteren führt die Hemmung der NMDAR – nicht aber die Aktivierung von 5-HT Rezeptoren – zu einer Reduktion der MMN Expression, was auf eine beeinträchtigte PE Verarbeitung hinweist. Interessanterweise zeigte sich, dass die MMN Expression unter Placebo prädiktiv und selektiv für das Ausmass der S-Ketamin-induzierten kognitiven Symptome ist. Unsere Ergebnisse weisen darauf hin, dass der glutamaterge

NMDA Rezeptor bei der Verarbeitung von PEs eine zentrale Stellung einnimmt und die Erfassung der MMN Expression einen wichtigen Beitrag zur Aufdeckung der Pathophysiologie kognitiver Störungen der Schizophrenie leisten kann. Dementsprechend könnte die Untersuchung der MMN Expression als Biomarker zur Früherkennung psychotischer Erkrankungen dienen und eine vielversprechende Grundlage zur Beurteilung neuer pharmakologischer Ansätze bei der Behandlung kognitiver Störungen schaffen.

Im *Kapitel 3* haben wir zudem einen computergestützten Modellierungsansatz verwendet, um zu prüfen, ob die gefundene NMDAR induzierte Reduktion der MMN Expression durch Veränderungen der effektiven Konnektivität innerhalb hierarchisch verbundenen auditiven Arealen erklärt werden kann. Das heisst, wir haben eine quantitative Konnektivitätsanalyse durchgeführt, um diejenigen Kopplungsparameter zu bestimmen, welche sich signifikant zwischen der Placebo- und der S-Ketamin-Bedingung unterscheiden und zudem prädiktiv für die Veränderungen von S-Ketamin induzierten Symptomen sind. Die Konnektivitätsanalyse ergab eine signifikante Reduktion der „bottom-up" Konnektivität infolge der S-Ketamin Verabreichung. Weiter konnte gezeigt werden, dass die reduzierte „bottom-up" Konnektivität signifikant die S-Ketamin induzierten kognitiven Defizite vorhersagt. Unsere Resultate suggerieren einen konkreten Mechanismus für die NMDAR induzierte Reduktion der MMN Expression, welcher mit der Psychopathologie unter Substanzeinfluss korreliert. Im Generellen weist diese Studie auf das Potential Model basierter Ansätze hin, um aus nicht-invasiven EEG-Daten den Beitrag der synaptischen Plastizität zur Generierung verschiedener Hirnaktivitäten zu quantifizieren.

Neben der experimentellen Verwendung psychotomimetischer Substanzen als pharmakalogische Modellpsychosen haben Studien in den 60ziger Jahren und neuere klinische Arbeiten gezeigt, dass Psilocybin und Ketamin stimmungsaufhellende und antidepressive Eigenschaften aufweisen. Genauer gesagt konnte gezeigt werden, dass Ketamin bei ansonsten therapieresistenten depressiven Patienten die Symptome innert Stunden verbessern kann, während Psilocybin bei Krebspatienten im Endstadium zu einer Stimmungsaufhellung führt und die Angst reduziert. Einige bildgebende Studien lassen vermuten, dass Ketamin und Psilocybin die Verarbeitung von emotionalen Reizen beeinflussen, indem sie die Informationsverarbeitung zwischen präfrontalen, limbischen und visuellen Hirnstrukturen modulieren. Allerdings ist die neuronale Grundlage der Ketamin- und Psilocybin-Wirkung auf die emotionale Informationsverarbeitung bislang noch nicht operationalisiert untersucht worden.

Zur weiteren Aufklärung der neuronalen Grundlagen der Ketamin und Psilocybin Wirkung auf die emotionale Reizverarbeitung haben wir im *Kapitel 4* dieser Arbeit untersucht, ob S-Ketamin und Psilocybin die visuell evozierten Ereignis-korrelierten Potentiale (EKP) P100 und N170 beeinflussen, wenn den Probanden unbewusst und bewusst emotionale Gesichter präsentiert wurden. Dabei scheint das Erkennen und die Verarbeitung von emotionalen Gesichtern nicht nur bei Gesunden für eine (optimale) soziale Interaktion von grundlegender Bedeutung zu sein, sondern dürfte auch, wie klinische Befunde vermuten lassen, in der Pathophysiologie der Depression eine wichtige Rolle spielen. Diese Ansicht wiederspielgelt sich auch in der Tatsache, dass emotionale Gesichter im Vergleich zu neutralen Gesichtern bei Gesunden im visuellen Kortex eine verstärkte neuronale

Aktivität hervorrufen. Dies ist auch zu beobachten, wenn die Gesichter unbewusst präsentiert und verarbeitet werden. Dementsprechend kann die Modulation visueller Aktivität durch emotionale Ausdrücke als eine grundlegende Regulation elementarer emotionaler Signale verstanden werden, welche in enger Verbindung mit unserer sozialen Kognition steht. Interessanterweise zeigen einige klinische Studien, dass depressive Patienten im Vergleich zu Gesunden vermehrt auf negative emotionale Reize fokussieren und auch verstärkt auf solche reagieren. Die Ergebnisse unserer Studie zeigen , dass beide Psilocybin und S-Ketamin die Reaktion auf emotionale visuelle Reize reduzieren, was sich in einer Abnahme der frühen visuellen N170 EKP ausdrückt, und dass diese Abnahme davon abhängt, ob das Gesicht unbewusst oder bewusst präsentiert wird. Desweitern hat unsere Auswertung ergeben, dass beide Substanzen das durch ängstliche Gesichter ausgelöste N170 EKP vergleichbar reduzieren. Hingegen scheint S-Ketamin, nicht aber Psilocybin, auch das durch glückliche Gesichter ausgelöste N170 EKP signifikant abzuschwächen. Unsere Resultate zeigen, dass die Aktivierung serotonerger Rezeptoren (5-$HT2_{A/1A}$) und die Hemmung glutamaterger NMDA Rezeptoren durch Psilocybin respektive S-Ketamin zu einer differentiellen Modulation der frühen emotionalen Gesichtsverarbeitung im visuellen Cortex führen. In Anbetracht dessen, dass depressive Patienten einen negativen emotionalen Bias zeigen, weist diese Studie auf das Potential von Psilocybin und Ketamin hin, um solchen negativen emotionalen Verarbeitungsneigungen entgegenzuwirken und im Falle von Psilocybin zudem die Verarbeitung von positiven Reizen nicht beeinträchtigt. In diesem Sinne kann die Erfassung von frühen visuell evozierten Potentialen eine physiologische Grundlage bietet, um pharmakologisch induzierte Veränderungen der emotionalen Verarbeitung zu erkennen und möglicherweise auch zu einem besseren Verständnis der pharmakologischen Mechanismen führt, welche der emotionalen Verarbeitung und deren Pathophysiologie unterliegen. Schlussendlich ermöglicht uns diese Studie eine Grundlage, um das klinische Potential beider Substanzen zur Behandlung affektiver Störungen weiter zu untersuchen.

1. General Introduction

Both the serotonergic (5-hydroxytryptamine, 5-HT) and glutamatergic (Glu) system have been implicated in the pathophysiology of different psychiatric disorders such as schizophrenia spectrum disorders, autism, addictive and obsessive compulsive disorders (OCD) as well as affective disorders (Elliott et al., 2011; Fontenelle et al., 2011; González-Maeso and Sealfon, 2009; McDougle et al., 2005; Ross and Peselow, 2009; Sanacora et al., 2008). Despite the large public health impact of schizophrenia (Casey et al., 2011; Saha et al., 2007) and depression (Andrade et al., 2003; Insel and Charney, 2003; Kessler et al., 2003), the specific contributions of 5-HT and glu to pathophysiological processes underlying both diseases remain poorly understood. Consequently, pharmacological treatments of depression and schizophrenia are often unsatisfactory and leave much to be desired. The majority of pharmacological treatments of depression contain the administration of selective serotonin re-uptake inhibitors (SSRI), however, response rates for these treatments are only modest and the participants who respond show an antidepressant effect not until eight weeks after the initial administration (Rush et al., 2006; Trivedi et al., 2006). Similarly, pharmacological treatments including the administration of antipsychotic drugs have been widely used for nearly half a century to treat schizophrenia, but there is little evidence that these treatments have substantially improved outcomes for most people with schizophrenia (Insel, 2010) and a precise relationship between the pharmacological mechanism of action and specific symptom formation has not been established.

The experimental research on psychedelic compounds might offer a suitable framework to gain more insights into the pathophysiology mechanisms underlying both diseases. Under this perspective, research on the pharmacological profile of serotonergic and glutamatergic psychedelics crucially contributed to several chemical hypotheses of schizophrenia. In particular, defining findings for these pharmacological models of schizophrenia were the discoveries of the psychosis-like symptoms induced by lysergic acid diethylamide (LSD), which predominantly activates 5-HT_{2A} receptors (5-HT_{2A}R) and by phencyclidine (PCP), a non-competitive N-methyl-D-aspartate receptor (NMDAR) antagonist (Geyer and Vollenweider, 2008; Javitt, 2010). Thus, NMDAR antagonists and 5-HT_{2A}R agonists constitute two classes of pharmacological models of psychosis that are used to study the neurobiology of psychotic symptom formation in schizophrenia.
Aside the established application of NMDAR antagonists and 5-HT_{2A}R agonists to model psychoses, research also carried out the use of psychotomimetics compounds as medical agents to treat mood and anxiety disorders (Vollenweider and Kometer, 2010). For example, studies in the late 1960s have been reported that NMDAR antagonists and 5-HT_{2A}R agonists provoke therapeutic effects in patients with anxiety and obsessive-compulsive disorders (OCD), depression and with terminal cancer (Geert-Jörgensen, 1968; Khorramzadeh and Lotfy, 1973; Pahnke et al., 1969). Recent evidence confirmed these findings by showing that the NMDAR antagonist ketamine produces rapid antidepressant effects in treatment-resistant depression (Diazgranados et al., 2010; Zarate et al., 2006), while the mixed 5-HT receptor agonist psilocybin enhances mood and decreases anxiety in terminal cancer patients within a month (Grob et al. 2011). Figure 1 shows a rough temporal overview of psychedelic research.

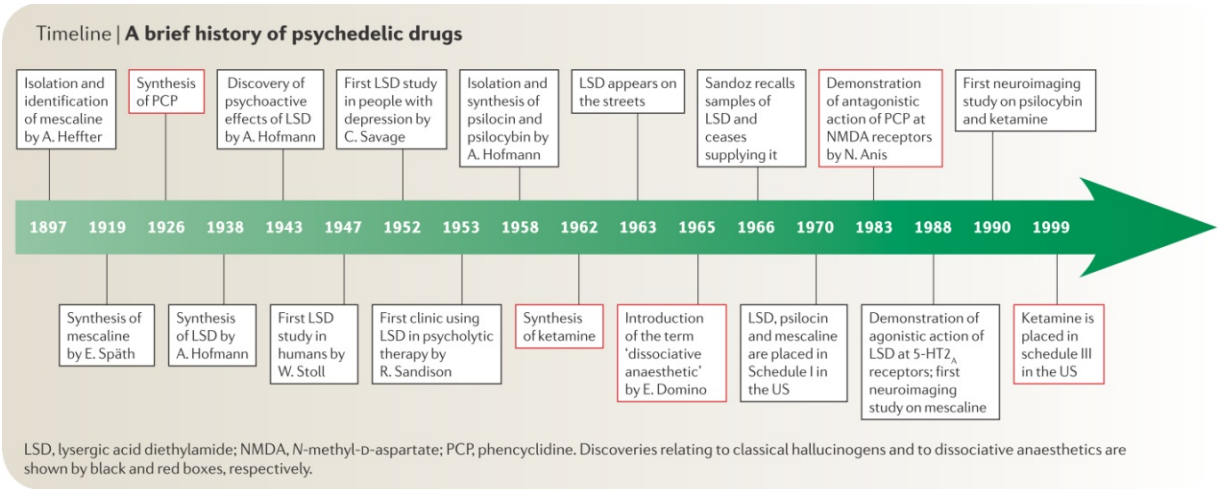

Figure 1 Benchmark data in psychedelic research referring to glutamatergic and serotonergic agents. Abbreviations: LSD: lysergic acid diethylamide; NMDA: N-methyl-D-aspartate; PCP: phencyclidine. Discoveries relating to classical hallucinogens and to dissociative anaesthetics are shown by black and red boxes, respectively. Adapted from Vollenweider and Kometer (2010).

Broadly speaking, exploring the effects of NMDAR antagonists and 5-HT_{2A}R agonists offer two perspectives in psychiatric research; on the one hand to produce psychosis-like symptoms in healthy volunteers, i.e. to model psychosis, and on the other hand to study further the role of serotonin and glutamate in emotional processing. In this thesis, I aim to outline two different frameworks i) to investigate further the neurophysiological mechanisms of psychotic symptom formation in these two pharmacological models of psychosis, which may be relevant for detecting early phases of the illness and might also serve as biomarker to assess the efficacy of novel pharmacological treatments, and ii) to investigate further the effect of psilocybin and ketamine on emotional processing and to identify its underlying neurophysiological basis, which may lead to the detection of pharmacologically induced changes in emotional processing and might also help to better understand the pharmacological mechanisms underlying emotional processing and its dysfunction in affective disorders.

1.1. The Role of Glutamate and Serotonin in Models of Psychosis and Schizophrenia

Recent research on schizophrenia has largely focused on neurobiological components of the disorder (Funk et al., 2011; Heckers, 2011; Smieskova et al., 2010). Although a huge amount of biological evidence could be found, schizophrenia lacks still robust relationships between neuronal correlates and psychopathological symptoms to specifically target pharmacological interventions.

Several pharmacological hypothesis and models of schizophrenia are inspired by the remarkable concordance of research on psychotomimetic compounds and their pharmacological profiles such as NMDAR antagonists and 5-HT_{2A}R agonists. Moreover, research on certain psychedelics has also contributed partly to the development of antipsychotic drugs. For example, the potential of ritanserin as an atypical antipsychotic has been revealed, inter alia, by its ability to block the LSD activity at 5-HT_{2A}Rs (Colpaert, 2003). Thus, understanding the pharmacological mechanisms of psychedelics and their contributions to the formation of psychotic symptoms provides important insight about the base for psychosis and might further facilitate the development of better pharmacological therapies for schizophrenia (González-Maeso and Sealfon, 2009). In more detail, NMDAR antagonists such as ketamine and classical hallucinogens like psilocybin, which predominantly activate 5-HT_{2A}R, constitute two pharmacological models of psychosis that are used to study the neurobiology of psychotic symptom formation in schizophrenia because they induce symptoms in healthy humans subjects that are highly reminiscent of those observed in schizophrenia (Geyer and Vollenweider, 2008; Javitt and Zukin, 1991; Kornhuber, 1990; Corlett et al., 2011). Table 1 depicts an overview of symptoms induced by NMDAR antagonists and 5-HT_{2A}R agonists in accordance with the symptomatology of schizophrenia. Although administration of ketamine to healthy humans reproduces positive and negative symptoms of schizophrenia including depersonalization phenomena (ego-disturbances and passivity phenomena), affective blunting and different aspects of disordered thoughts and cognition (Adler et al., 1999; Gouzoulis-Mayfrank et al., 2005; Krystal et al., 1994; Malhotra et al., 1996; Vollenweider et al., 1997a), psilocybin elicits more positive symptoms comparable to those in schizophrenia like profound changes in mood states, thought, intuition and experience of self (Geyer and Vollenweider, 2008; Gouzoulis-Mayfrank et al., 1998). During such states, perceptual hypersensitivity, illusion and visual hallucinations are common.

Despite this specific dissociation in symptoms induced by NMDAR antagonists and 5-HT_{2A}R agonists, they also share some common symptoms including positive symptoms. Both classes of drugs increase extracellular glutamate in PFC (Moghaddam et al, 1997; Muschamp et al, 2004), which may explain some of the common psychotic symptoms. However, while the pharmacological properties of these psychotomimetic compounts are well documented (Fantegrossi et al, 2008; Nichols, 2004), the neuronal and cognitive mechanisms underlying ketamine- and psilocybin-induced symptoms are less well understood. Based on theoretical concepts (Corlett et al., 2011; Friston, 2005a; Stephan et al., 2006; Stephan et al., 2009), in the following I outline a conceivable approach to study ketamine- and psilocybin-induced symptoms by embedding the drug-induced psychosis-like symptoms in a cognitive model referring to learning and inference.

Table 1 Comparison of effects of serotonergic hallucinogens (psilocybin), NMDAR antagonists (ketamine), and symptoms in schizophrenia.

	Psilocybin	Ketamine	Schizophrenia
Primary focus of action	5-$HT_{2A/1A}$, GABA, $DA_{2/1}$	NMDA, 5-HT_{2A}, GABA, $DA_{2/1}$	unknown
Positive symptoms			
Hallucinations/Illusions	+ +	+	+ +
Delusions	+	+	+ +
Thought disorders	+	+ +	+ +
Negative symptoms			
Blunted affect	0 - +	+ - + +	+ +
Withdrawal	+	+ - + +	+ +
Depersonalization	+ - + +	+ +	+ +
Derealization	+	+ +	+ +
Neuropsychology			
Attention disturbances	+ - + +	+	+ +
Distractibility	+	+ +	+ +
Working memory	+	+ +	+ +
Associative deficits	+	+ - + +	+ +
Planning/mental	+ +	?	+ +

Abbreviations: 5-HT: 5-hydroxytryptamine; NMDA: N-methyl-D-aspartate; DA: dopamine; GABA: gamma-Aminobutyric acid. Adapted from Vollenweider et al. (2001).

According to associative learning theories, it has repeatedly been proposed that both natural and drug-induced psychosis can be explained by the concept of predictive coding (Corlett et al., 2009; Corlett et al., 2011; Fletcher and Frith, 2009; Gray et al., 1991; Hemsley, 1993). This concept refers to predictive coding models of learning and inference, which rest on empirical Bayes (Friston, 2005a). In that article, the author provides a model how cortical responses can be understood as expressions of prediction errors (PE), which indexes learning and inference processes in the brain. Within this general framework, the brain's architecture is hierarchically organized, so that the formed PE in lower-level systems passes forward to higher-level systems. Simultaneously, the lower-level systems receive feedbacks from higher-level systems to predict further sensory input. In other words, each neuronal system within the task-related hierarchy receives bottom-up input about the state of the level below and top-down predictions from the level above. A PE emerges when the actual input does not match with the prediction about it, i.e. when the existing model has not fully accounted for the input (Fletcher and Frith, 2009). PE represents an alert system, which suggests that the current model is wrong. During learning and inference, predictions and PE are adjusted in order to minimize PE at all levels of the hierarchy. This assumes updates of our internal models of the environment so that potentially surprising events can be predicted. Such a scheme has been used to explain the genesis of evoked brain responses like early visual cortical responses (Murray et al., 2002; Rao and Ballard, 1999) and auditory mismatch responses (Baldeweg, 2006; Baldeweg et al., 2004; Garrido et al., 2009a).

Therefore, PE constitutes a driving force for learning, because they signal the need for learning in order to update predictions (Schultz et al., 1997). Defining for this thesis, it has been posited that the Bayesian passing scheme of PE processing is aberrant in schizophrenia patients (Fletcher and Frith, 2009; Stephan et al., 2006; Stephan et al., 2009), and specifically leads to the formation of positive symptoms such as delusions or hallucinations (Fletcher and Frith 2009). Recent studies began to elucidate the precise location of PE signals in the brain associated with positive symptom formation in drug-induced and naturally occuring psychosis. In a first work, Corlett and colleagues (2006) demonstrated that low-dose of ketamine disrupted the PE-dependent learning activity in the right prefrontal cortex (rPFC). Notably, the activity in the rPFC to PE under placebo i.e. without any drug intake was positively correlated with ideas of references under ketamine (Figure 2A). Along this line, the same procedure was translated into a patient study. This study revealed, analogue to the ketamine study, that PFC responses in the patient group were suggestive of disrupted PE processing, and that the extent of PE disruption was significantly related to an individual's propensity to delusion formation (Corlett et al., 2007) (Figure 2B). Shortly speaking, NMDAR-mediated aberrant PE processing in the PFC may reflect a mechanism for the emergence of psychotic symptoms in schizophrenia in general and in particular of positive symptoms.

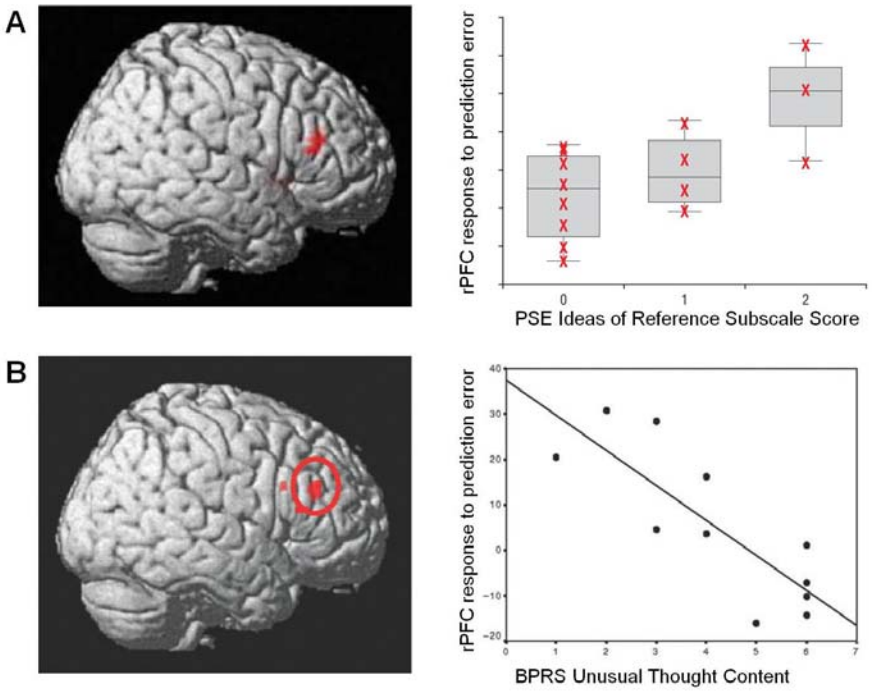

Figure 2 A) The left panel shows brain regions in which the level of error-dependent response predicted the score for simple ideas of reference under ketamine. The right panel shows a plot of this relationship, with rPFC activity summarized as a box plot for each of the ratings on the Present State Examination. Adapted from Corlett et al. (2006). **B)** Relating brain response to prediction error with delusion formation in schizophrenia patients. The rendered image highlights a region of right lateral prefrontal cortex, the activity of which correlates across patients with their delusion severity at the time of scanning. Adapted from Corlett et al. (2007).

As already mentioned, predictions and PE are adjusted during learning and inference in order to minimize PE at all levels of the hierarchy. Critically, this adjustment is conveyed via synaptic connections (plasticity) among all levels of the neuronal hierarchy. In consequence, aberrant coupling or interactions within a task-related network could be due to impairments in synaptic transmission and plasticity, which is thought to be a key pathophysiological hallmark of schizophrenia (Friston, 1998; Stephan et al., 2006; Stephan et al., 2009). Recent studies examined the hypothesis of disconnection by investigating temporally coherent brain activity from functional magnetic resonance imaging (fMRI) data. In particular, they reported aberrant fronto-temporal connectivity in schizophrenia patients relative to healthy subjects (Allen et al., 2010; Diaconescu et al., 2011; Lawrie et al., 2002; Winder et al., 2007), what could be expressed at a cognitive level as a failure to integrate perception and action (Friston and Frith, 1995). This corresponds nicely with previous evidence showing that administration of both ketamine and psilocybin alters the fronto-temporal circuitry associated with depersonalization and thought disorder (Nagels et al., 2011a; Nagels et al., 2011b; Vollenweider et al., 1997a; Vollenweider et al., 1997b). Along this line, it is assumed that disrupted NMDAR-mediated synaptic plasticity due to abnormal regulation of NMDARs by neuromodulatory transmitters like 5-HT may underlie disordered brain connectivity, which leads to the manifestation of psychotic symptoms in schizophrenia patients (Stephan et al., 2006). Indirect support for NMDAR-mediated abnormal synaptic plasticity in schizophrenia is further provided by genetic studies. Specifically, it has been shown that six of the seven candidate genes for schizophrenia are intimately related to NMDAR-dependent signaling (Harrison and Weinberger, 2005). However, the disconnection hypothesis of schizophrenia suggests that it is not NMDAR-mediated synaptic plasticity per se that is abnormal, but its modulation during reinforcement and perceptual learning, reflected in the inability to form new stimulus-stimulus associations, leading to a disruption of perceptual learning and inference (i.e., perceptual dysmetria) (Friston, 2005b). Put simply, psychotic symptom formation in schizophrenia may result from disrupted learning performances due to abnormal NMDAR-mediated synaptic plasticity within a task-related network, which is linked with the vulnerability to the formation of psychotic symptom.

One of the most attractive paradigms for studying synaptic plasticity during implicit perceptual learning is the mismatch negativity (MMN) event-related potential (ERP) (Friston, 2005a; Garrido et al., 2009b; Todd and Robinson, 2010). The MMN is an electrophysiological event-related change (or regularity-violation) detection to auditory stimuli (deviants) that differ in a physical stimulus dimension from a sequence of preceding identical standards (Näätänen et al., 1978). The maximum peak difference between the standard and the deviating tone occurs over temporal and frontal areas at approximately 180 ms (Figure 3). The MMN is elicited in the absence of subject's attention, providing a reliable paradigm in clinical populations. Indeed, the MMN is of particular interest in schizophrenia research, because deficits in the MMN amplitude have repeatedly been reported in schizophrenic patients (Umbricht and Krljes, 2005), making the MMN to one of the most strongly replicated biomarker of cognitive dysfunction in schizophrenia (Javitt et al., 2008). Moreover, the MMN appears to detect the transition of 'ultra-high risk' to first-episode psychosis (Atkinson et al., 2011; Bodatsch et al., 2010; Orosz et al., 2011; Shin et al., 2009), suggesting the potential of the MMN in predicting psychosis risk.

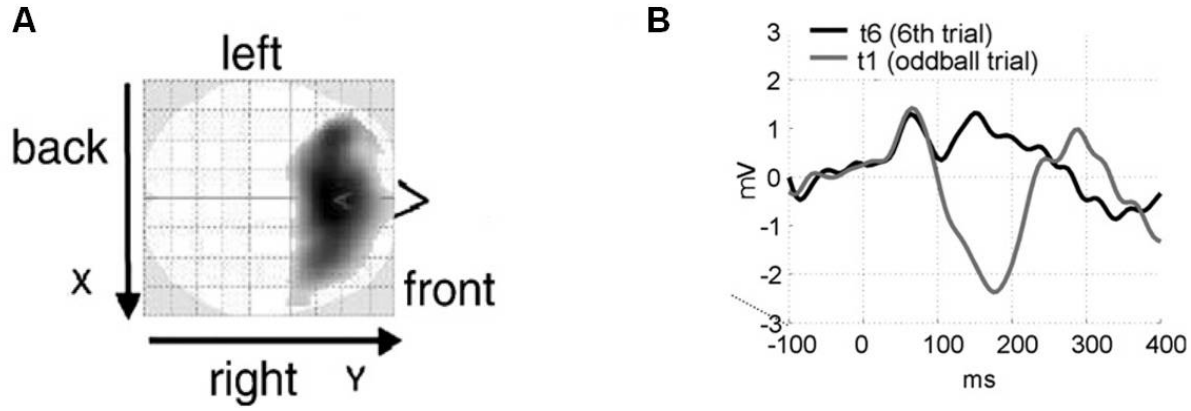

Figure 3 A) Significant effects between the standard and the deviating tone were found over temporal and frontal areas in the time range of 110 to 200 ms, peaking at 180 ms. **B)** Grand mean (averaged over all subjects) ERP responses to the sixth tone presentation, the established "standard" (t_6 in black) and deviant tone (t_1 in gray) at fronto-central electrodes where the MMN response peaks at about 180 ms from change onset. Adapted from Garrido et al. (2008).

The neuronal mechanism underlying the MMN generation is controversially discussed. In accordance with classical theories (Näätänen, 1992), the MMN potential arises whenever there is a break of regularity in a structured auditory sequence, generated by a fronto-temporal network comparing the actual sensory input with the already established memory trace of preceding standard stimuli (Doeller et al., 2003; Opitz et al., 2002; Rinne et al., 2000). This is the so-called model-adjustment hypothesis (Winkler et al., 1996). However, this notion has been challenged previously by proposing that the MMN emerges exclusively from local neuronal adaptation in the auditory cortex (Jääskeläinen et al., 2004), the so-called adaptation hypothesis. A more recent study used Dynamic Causal Modeling (DCM) to estimate plausible connectivity graphs underlying the MMN and suggests that the model explaining the MMN amplitude best was a model that accommodates intra-areal (local) adaptation within the primary auditory cortex combined with plasticity of inter-areal connections between temporal and frontal regions (Garrido et al., 2008). The authors explicitly interpreted their findings within the predictive coding framework, emphasizing that this theory includes both adaptation and model adjustment in the sense that "model adjustment" corresponds to the adjustment of a generative model for future stimuli and "adaptation" corresponds to local changes in post-synaptic gain (Garrido et al., 2008). Furthermore, there is strong evidence that the MMN depends critically on synaptic plasticity (Baldeweg, 2006; Stephan et al., 2006). In particular, schizophrenia patients show impairments at frontal but not temporal components of the MMN (Baldeweg et al., 2002; Sato et al., 2003), which may reflect aberrant coupling between temporal and frontal areas. Consistent with the results in schizophrenia patients, studies using ketamine also reported reduced frontal but not temporal MMN amplitudes (Heekeren et al., 2008; Umbricht et al., 2000) (Figure 4). Hence, the MMN is a promising paradigm to study PE processing during implicit perceptual learning within a bidirectional connected

hierarchical architecture, which coupling may rest on NMDA-dependent synaptic plasticity and its regulation by modulatory transmitters like 5-HT(Friston, 2005a).

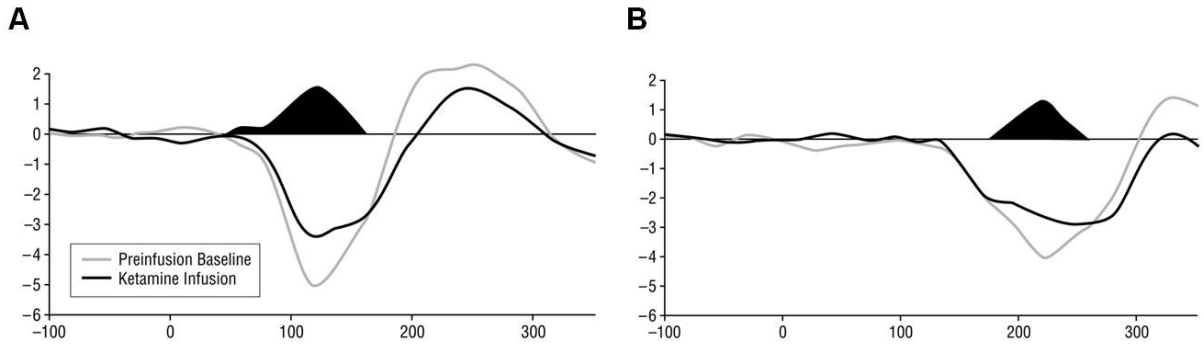

Figure 4 Effects of ketamine on the MMN (difference wave: deviant - standard) in the pitch **A)** and duration **B)** deviance condition. The gray lines represent the MMN wave before ketamine administration; the black line, the MMN wave under ketamine; and the dark area, the difference between the 2 curves (ie, the reduction of MMN during ketamine administration). Adapted from Umbricht et al. (2000).

Given the above, in *chapter 2* of this thesis we challenged subjects with a psychological task (MMN), which engages a specific cognitive process (implicit perceptual learning). We further indexed this cognitive process with a physiological brain marker, and finally relate the individual baseline marker to the subjective variability in pathophysiological experiences they had (psychotic symptoms). Such a principle is suitable to test hypotheses about the cognitive and neural bases of specific symptoms (Brown, 2011; Corlett et al., 2011; Honey et al., 2008). In particular, we investigated (i) whether the MMN encoding of PE is affected by the NMDAR antagonist S-ketamine and the preferential 5-HT_{2A}R agonist psilocybin using a roving MMN paradigm and (ii) whether the encoding of PE under placebo can be used to predict specific drug-induced symptoms. Based on the functional anatomy underlying the MMN generation (Garrido et al., 2008), in *chapter 3* we provide a model-based approach (DCM) to understand the obtained results of *chapter 2* by investigating effective connectivity within the network underlying the MMN generation. DCM is an established technique to estimate how ERPs (e.g. MMN) result as an output of causal dynamics between coupled neural systems (e.g. temporal and frontal MMN sources) and how these cortico-cortical connections are modulated by experimental manipulations (Friston et al., 2003). This means that opposed to functional connectivity, DCM uses the concept of effective connectivity, which describes the influence one neural system exerts over another (Friston, 1994). DCM uses a biologically informed causal model to make inferences about the underlying neural mechanisms that generates the observed event-related responses. This approach provides an important advancement over conventional source reconstruction techniques of ERP data, because it places neurobiological constraints on the model inversion, in which the parameters of the reconstruction have a specific neuronal interpretation. The parameters thus encode the coupling among sources and how coupling depends upon stimulus attributes or experimental manipulations

(David et al., 2006; Kiebel et al., 2006). Therefore, DCM is a useful approach to study neuromodulation and synaptic plasticity (Stephan et al., 2010).

1.2. The Role of Glutamate and Serotonin in Emotional Processing

The crucial role of 5-HT in emotional processing is evidenced by pharmacological and genetic studies (Elliott et al., 2011; Sharp and Cowen, 2011). It's a long-standing theory that a breakdown in 5-HT transmission is strongly implicated in the pathophysiology of affective disorders such as depression (Sharp and Cowen, 2011). In consequence, compounds that inhibit the 5-HT re-uptake and thereby increasing 5-HT brain level have been used to treat depression for more than 40 years such as SSRIs (Harmer, 2008). Figure 6 shows the neurobiological and neuropsychological effect of increased 5-HT brain levels. SSRIs are certainly safe and relatively easy to use, but do not exhibit rapid effects (Skolnick et al., 2001). In more detail, almost one-third of patients with depression achieve remission after SSRI treatment using citalopram, and the participants who respond show an antidepressant effect not until 8 weeks after the first administration (Trivedi et al., 2006). This delay period of action may have devastating effects, because high rates of mortality and morbidity are present during this period (Machado-Vieira et al., 2008).

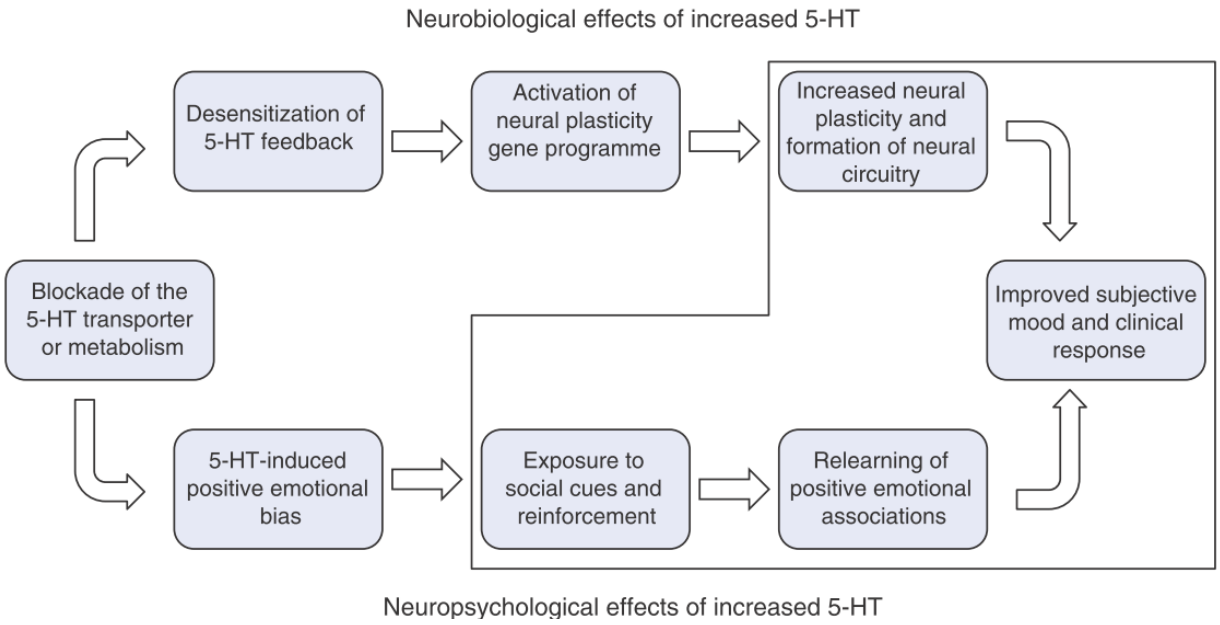

Figure 6 Illustration of adaptive neurobiological and neuropsychological processes following several weeks of SSRI treatment. The induction of a positive emotional bias occurs after acute treatment and forms the basis for the gradual relearning of positive emotional associations. As indicated by the framed box, the increase in neural plasticity and formation of neural circuits occurs within emotional processing networks to allow positive emotional stimuli (e.g. social cues) to act and to be relearned and bring about improved mood. Adapted from Sharp and Cowen (2011).

Previous research has also been focused on the application of psychedelics as therapeutic agent to treat affective disorders. In this view, recent data showed that psychedelics modulate neural circuits that have been implicated in mood and affective disorders, and can reduce the clinical symptoms of these disorders (Vollenweider and Kometer, 2010). For example, convincing evidence in the

1960s have already suggested a therapeutic benefit of classical hallucinogens such as LSD and psilocybin in the treatment of OCD (Brandrup and Vanggaard, 1977; Leonard and Rapoport, 1987; Moreno and Delgado, 1997) alcoholism (Kurland et al., 1967) and cluster headache (Sewell et al., 2006), as well as to treat pain in terminal cancer patients (Pahnke et al., 1969). Motivated by these early findings in the sixties, previous works confirmed that psilocybin acutely reduced OCD symptoms in treatment-resistant patients (Moreno et al., 2006) and produced a gradual reduction of anxiety in advanced-stage cancer patients within a month (Grob et al., 2011). Furthermore and crucial for therapeutic agents, there were no clinically significant adverse events following psilocybin administration in patients. In healthy subjects, the effect of psilocybin at low to medium doses is characterized by distinct altered states of consciousness including changes in mood states (Geyer and Vollenweider, 2008). In particular, acute psilocybin administration in healthy subjects leads to heightened mood, increased emotional excitation and sensitivity (Studerus et al., 2010b). Importantly, administration of psilocybin to healthy, well-instructed volunteers in the context of a carefully monitored research environment provides acceptable level of risk (Studerus et al., 2010b). The molecular mechanism of psilocybin is not fully understood. Findings from animal studies proposed that psilocybin might produce his effects primarily through agonistic actions at cortical 5-HT_{2A}R (Aghajanian and Marek, 1999; Aghajanian and Marek, 1997; González-Maeso and Sealfon, 2009). Furthermore, activation of 5-HT_{2A}R by psilocybin leads to robust glutamate-dependent increase in the activity of pyramidal neurons, preferentially those in layer V of the prefrontal cortex (Béïque et al., 2007). It has been suggested that the psilocybin-induced glutamate release is triggered by stimulation of postsynaptic 5-HT_{2A}R on a subpopulation of pyramidal cells in the deep layers of the PFC (Béïque et al., 2007; Puig et al., 2003). Figure 7 shows a rough overview of psilocybin's mechanism of action.

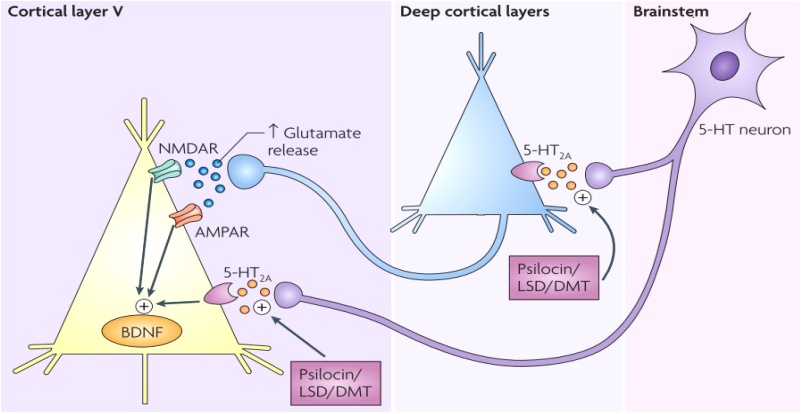

Figure 7 Activation of the prefrontal network and glutamate release by classical hallucinogens. The figure shows a model in which psilocybin, LSD and dimethyltryptamine (DMT) increase extracellular glutamate levels in the prefrontal cortex through stimulation of postsynaptic 5-HT_{2A}R that are located on large glutamatergic pyramidal cells in deep cortical layers (v and vi) projecting to layer v pyramidal neurons. This glutamate release leads to an activation of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) and NMDAR on cortical pyramidal neurons. In addition, hallucinogens directly activate 5-HT_{2A}R located on cortical pyramidal neurons, might be leading to an

increased expression of brain-derived neurotrophic factor (BDNF). Adapted from Vollenweider and Kometer (2010).

Aside the well established role of the 5-HT system in the pathophysiology of affective disorders (Elliott et al., 2011; Sharp and Cowen, 2011), more recent research these days focus on the glutamate system (Sanacora et al., 2008; Skolnick et al., 2009). According to animal data from the inescapable stress paradigm introduced by Shors and colleagues (1989), exposure to inescapable stress, which induces a syndrome of behavioral depression that is antagonized by clinically effective antidepressants (Desan et al., 1988; Shanks and Anisman, 1989), impaired the induction of NMDAR-dependent long-term potentiation in the hippocampus. Based on these findings, it was first hypothesized that the NMDAR could be involved in modulating the behavioral deficits induced by inescapable stressors (Trullas and Skolnick, 1990). This hypothesis was explored by examining the effects of compounds that reduce transmission at NMDAR in different animal models of depression, i.e. by NMDAR antagonists (Papp and Moryl, 1993; Papp and Moryl, 1994a; Papp and Moryl, 1994b). Translated into human studies, increasing evidence revealed that the NMDAR antagonist ketamine has rapid antidepressant effects in depressed patients (Berman et al., 2000; Diazgranados et al., 2010; Zarate et al., 2006), in contrast to the late occuring effect of SSRIs. Specifically, a single dose of ketamine in treatment-resistant patients with depression and bipolar depression resulted in a rapid (hours) and significant antidepressant effect, which sustained for about one week (Diazgranados et al., 2010; Zarate et al., 2006). Importantly, subanesthetic doses of ketamine to humans is not associated with physical dependences (Britt and McCance-Katz, 2005), and an increased risk of more protracted psychosis in both healthy (Perry et al., 2007) and patients (Carpenter, 1999). The molecular mechanism underlying ketamine's rapid antidepressant effect is focus of current research. It has been suggested that acute ketamine exposure blocks NMDAR and facilitates glutamate release by decreasing GABAergic inhibitory feedback in pyramidal cells (Homayoun and Moghaddam, 2007), what further translate into increased AMPAR throughput, which is probably determining for the subjective and rapid antidepressant effect of ketamine (Vollenweider and Kometer, 2010) (Figure 8).

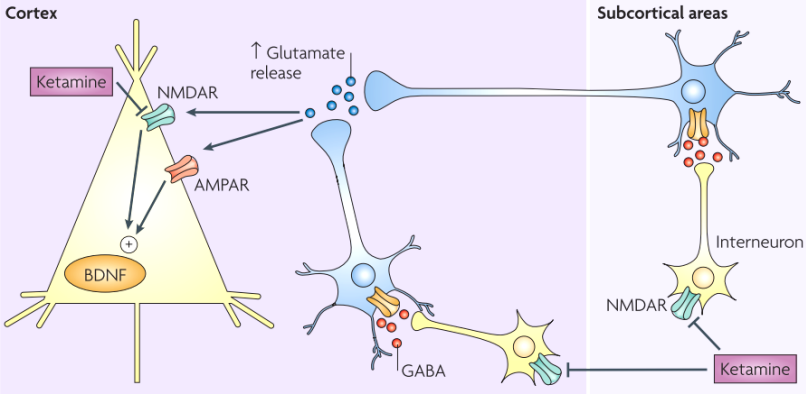

Figure 8 Activation of the prefrontal network and glutamate release by ketamine. The figure shows a model in which ketamine blocks inhibitory GABAergic interneurons in cortical and subcortical brain areas, leading to enhanced firing of glutamatergic projection neurons and increased extracellular

glutamate levels in the prefrontal cortex. As ketamine also blocks NMDAR on cortical pyramidal neurons, the increased glutamate release in the cortex is thought to stimulate cortical AMPA more than NMDA receptors. The increased AMPAR-mediated throughput relative to NMDAR-mediated throughput is thought ultimately to lead to increased expression of BDNF. Adapted from Vollenweider and Kometer (2010).

More recent animal studies have extensively investigated the molecular action of ketamine and revealed exciting new findings (Autry et al., 2011; Li et al., 2010). Nevertheless, further studies are needed to precisely understand the exact molecular mechanism of ketamine's rapid antidepressant action. Although the molecular mechanisms underlying psilocybin's and ketamine's actions are currently being investigated in animal studies, however, the acute effects of both drugs on emotional processing in humans are less well understood. In the following, I provide a concept how both drugs can be used to study acute serotonergic and glutamatergic effects on emotional processing and to further investigate the potential of both drugs to treat affective disorders. In particular, we were particularly interested in investigating how acute serotonergic and glutamatergic manipulations modulated emotional processing biases. Such an approach provides a useful framework to disentangle pharmacological mechanisms of emotional processing biases and its dysfunctions in affective disorders, as well as to assess the efficacy of novel therapeutic treatments to resist such dysfunctional emotional biases.

Facial expressions are critical signals of affective states and tasks referring to the recognition of other's people facial expressions provide a useful framework to study emotional processing biases both in healthy subjects and in relation to affective disorders. When we see a face, we confer and infer the state of mind of ourselves and of our peers to permit highly adaptive social behavior. The critical importance of face recognition in the human social functioning is shown by the fact that emotional faces can be processed without conscious awareness (Smith, 2011). Along this line, Ekman and Friesen (1971) already proposed that there are six basic emotional face expressions, which could be recognized among different cultures, namely happy, sad, fearful, angry, disgusted and surprised faces (Figure 6).

Figure 6 Six basic facial expressions proposed by Ekman and Friesen (1971), which are constant across cultures. From left to right: Anger, fear, disgust, surprise, happiness, sadness.

Of clinical relevance, several affective disorders are accompanied by deficits in the recognition of other people's emotion from their facial expression (dysfunctional emotional biases). In particular, facial processing biases towards the processing of negative and away from positive facial expressions are key impairments in depression (Beck, 2008; Surguladze et al., 2004). Notably, such dysfunctional facial processing biases actually occur not only from deficits in conscious recognizing of facial expressions (Joormann and Gotlib, 2006) but also from deficits during non-conscious emotion processing (Yang et al., 2011)

The neuronal network underlying emotional face processing has been well studied in healthy volunteers and involves the same circuitry that has been implicated in fear and anxiety responses in humans (Shin and Liberzon, 2010). Generally, emotional faces increase neuronal activity in a distributed network including visual cortical, limbic and prefrontal regions, as well as regions of the reward circuitry, including the ventral striatum and the prefrontal cortex (Ishai, 2007; Ishai et al., 2005; Phan et al., 2002). In particular, increased brain responses to emotional relative to neutral faces have been observed within visual face-selective areas of the brain, even when emotional facial expressions are masked to prevent conscious awareness (Anderson et al., 2011; Demenescu et al., 2011; Kleinhans et al., 2011) (Figure 7). In this view, modulations of face-selective responses in the visual cortex by emotional expressions have been interpreted as fundamental regulation of basic emotional signals closely associated with social appraisal and cognition (Schultz et al., 2003; Singer et al., 2004). Face-selective regions in the visual cortex can thus be viewed as core components of the "social brain" (Schultz et al., 2003). However, while numerous studies are currently investigating the neuronal pathways of conscious and non-conscious emotional processing (Pessoa and Adolphs, 2010; Tamietto and de Gelder, 2010), it is less well understood how visual responses to emotional facial expressions are altered under specific pharmacological manipulations during conscious and non-conscious processing.

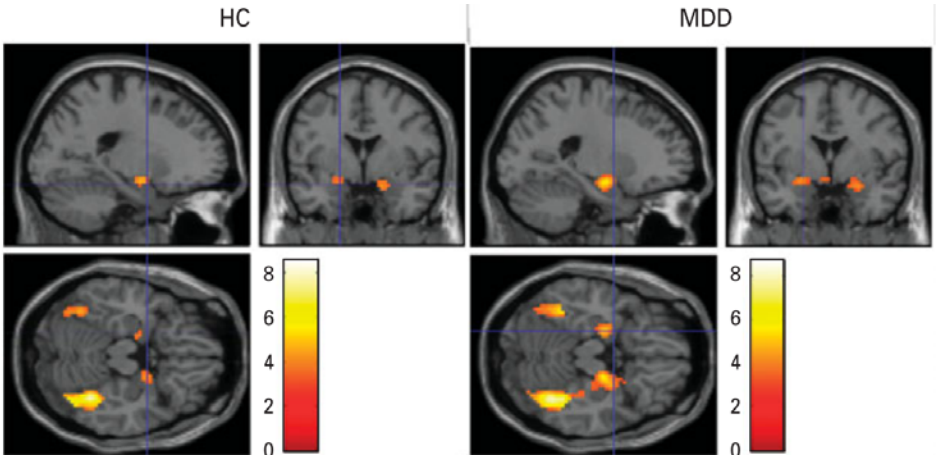

Figure 7 Main effects of viewing photographs of faces (> scrambled faces) within controls and depressed patients. Main activations were in the fusiform gyrus and amygdala. Color bar indicates t value. Abbrivations: HC, healthy controls; MDD, major depression. Adapted from Demenescu et al. (2011).

Emotional face processing is modulated both by 5-HT (Elliott et al., 2011), and glutamate (Abel et al., 2003). The 5-HT system is of considerable relevance because cortical regions affected by 5-HT manipulation overlap with those regions associated with emotional processing (Smith et al., 2002). For example, administration of the SSRI citalopram increases the recognition of happy and fearful faces in healthy volunteers (Browning et al., 2007; Harmer et al., 2003). Interestingly, imaging studies revealed that SSRI administration acutely increased fusiform gyrus (FG) activity to aversive stimuli in healthy volunteers (Del-Ben et al., 2005; McKie et al., 2005), what might partly mediate the increase in fear recognition after a single SSRI dose. Noteworthy, the FG represents an important visual face-selective area of the brain. Thus, acute SSRI administration affects the processing of social relevant cues by modulating visual responses in face-selective area of the brain. In addition, emotional processing can also be modulated by glutamate. Specifically, a previous fMRI study revealed that following ketamine administration, fearful faces no longer activate the amygdala and other limbic regions, and that FG activity in response to fearful faces is significantly reduced compared to placebo (Abel et al., 2003). All together, these data in healthy subjects indicate that acute serotonergic and glutamatergic manipulations change emotional processing as indexed by the assessment of visual cortex responses to emotional facial expressions.

A suitable method to assess visual activity in response to emotional facial expressions even during non-conscious processing provides the recording of visual ERPs (Liddell et al., 2004; Pegna et al., 2008; Smith, 2011; Williams et al., 2004). Two ERPs with selective responses to emotional relative to neutral faces are the P100 and N170 ERP (Fichtenholtz et al., 2009; Pegna et al., 2008; Smith, 2011) (Figure 8).

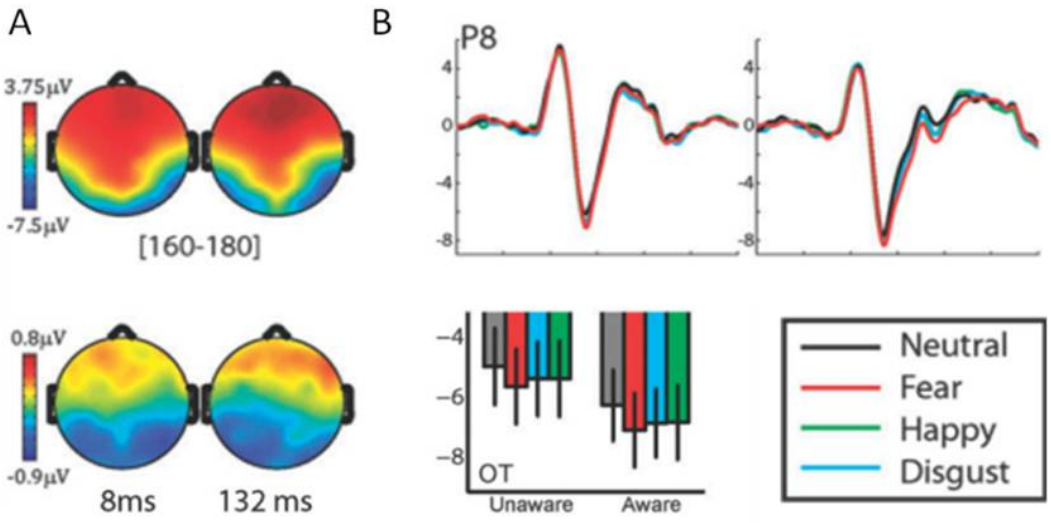

Figure 8 A) Topography of the N170 ERP signal evoked by the presentation of the faces, averaged across all expressions, in each of the selected time windows for the 2 temporal delay conditions [8, 132 ms]. **B)** N170 ERP responses to emotional vs. neutral faces over electrodes P8 during non-conscious (8 ms) and conscious processing (132 ms). Bar charts indicate the averaged ERP for each expression. Adapted from Smith (2011).

The P100 ERP reflects rapid extraction of information related to emotion or salience that occurs before more fine-grained perceptual analyses are completed (Vuilleumier and Pourtois, 2007). Modulation of the P100 ERP has been shown with fearful (Fichtenholtz et al., 2009; Pourtois and Vuilleumier, 2006), angry (Santesso et al., 2008), and positive expressions (Batty and Taylor, 2003; Brosch et al., 2008). The later N170 ERP is associated with structural encoding of facial configurations (Itier and Taylor, 2004) and is highly correlated with FG activity (Deffke et al., 2007; Sadeh et al., 2010). The N170 ERP is also increased for a broad spectrum of emotional facial expressions relative to neutral ones (Blau et al., 2007; Leppänen et al., 2007), even during conscious processing (Pegna et al., 2008; Smith, 2011).

Given this background, in *chapter 4* of this thesis we used emotional facial expressions to investigate further the neuronal underpinnings of the effect of psilocybin and S-ketamine on emotional processing using backward masking procedures. Backward masking is a key experimental paradigm for investigating sensory unawareness, because this method interferes with the activity in the ventral occipito-temporal cortex, an area, which is highly relevant for visual awareness (Macknik and Livingstone, 1998; Tamietto and de Gelder, 2010). The concept of backward masking supposes that the mask, which is present after the target face, interrupts the processing of the target face (Morris et al., 1996; Morris et al., 1998; Whalen et al., 1998). We first examined whether psilocybin and S-ketamine affect early visual ERP responses to facial expressions in a valence specific manner, and second whether these effects vary as a function of visual awareness. Specifically, signal detection theory was applied to establish objective threshold for conscious awareness irrespective of subject's response bias. Furthermore, early visually evoked ERP responses to fearful, happy and neutral faces were quantified by the P100 and N170 ERP during non-conscious compared to conscious processing.

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2. Mismatch Negativity Encoding of Prediction Errors Predicts S-ketamine-induced Cognitive Impairments

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AS, MK, KES, and FXV contributed to the study design of this paper. PAC and AS developed the MMN roving paradigm. AS and RB contributed to the conduction of the experiments and AS analyzed the data. AS contributed to the writing of the manuscript, with additional contributions by RB, MK, PAC, KES, ES, and FXV, who appears as co-authors in the published paper.

Abstract

Psychotomimetics like the N-methyl- D -aspartate receptor (NMDAR) antagonist ketamine and the 5-hydroxytryptamine2A receptor (5-HT 2A R) agonist psilocybin induce psychotic symptoms in healthy volunteers that resemble those of schizophrenia. Recent theories of psychosis posit that aberrant encoding of prediction errors (PE) may underlie the expression of psychotic symptoms. This study used a roving mismatch negativity (MMN) paradigm to investigate whether the encoding of PE is affected by pharmacological manipulation of NMDAR or 5-HT 2A R, and whether the encoding of PE under placebo can be used to predict drug-induced symptoms. Using a double-blind within-subject placebo-controlled design, S-ketamine and psilocybin, respectively, were administrated to two groups of healthy subjects. Psychological alterations were assessed using a revised version of the Altered States of Consciousness (ASC-R) questionnaire. As an index of PE, we computed changes in MMN amplitudes as a function of the number of preceding standards (MMN memory trace effect) during a roving paradigm. S-ketamine, but not psilocybin, disrupted PE processing as expressed by a frontally disrupted MMN memory trace effect. Although both drugs produced positive-like symptoms, the extent of PE processing under placebo only correlated significantly with the severity of cognitive impairments induced by S-ketamine. Our results suggest that the NMDAR, but not the 5-HT 2A R system, is implicated in PE processing during the MMN paradigm, and that aberrant PE signaling may contribute to the formation of cognitive impairments. The assessment of the MMN memory trace in schizophrenia may allow detecting early phases of the illness and might also serve to assess the efficacy of novel pharmacological treatments, in particular of cognitive impairments.

Keywords: model psychosis; NMDAR; 5-HT; predictive coding; MMN memory trace effect; cognitive impairment

Introduction

Dissociative N-methyl-D-aspartate receptor (NMDAR) antagonists such as ketamine and classic hallucinogens like psilocybin, which activate 5-hydroxytryptamine2A receptors (5-HT_{2A}R) constitute two models of psychosis that are used to study the neurobiology of psychotic symptom formation in schizophrenia (González-Maeso and Sealfon, 2009; Javitt and Zukin, 1991; Vollenweider and Geyer, 2001). While administration of ketamine to healthy volunteers reproduces both positive and negative symptoms of schizophrenia (Adler et al., 1999; Malhotra et al., 1996; Vollenweider et al., 1997a), psilocybin engenders positive symptoms that are highly reminiscent of those observed in schizophrenia (Geyer and Vollenweider, 2008; Gouzoulis-Mayfrank et al., 1998). In neuroimaging studies, both ketamine and psilocybin altered the activity in frontotemporal regions associated with depersonalization and thought disorder (Vollenweider et al., 1997a; Vollenweider et al., 1997c). Furthermore, ketamine infusion in schizophrenia patients transiently exacerbated positive symptoms (Lahti et al., 1995b) associated with an activation of PFC and thalamic structures (Lahti et al., 1995a). Although ketamine- and psilocybin-like drugs differ in their primary mechanism of action, both classes of drugs increase extracellular glutamate in PFC (Moghaddam et al., 1997; Muschamp et al., 2004), which may explain some of the common psychotic symptoms. However, while the pharmacological properties of these psychotomimetics are well documented (Fantegrossi et al., 2008; Nichols, 2004a), the neuronal and cognitive mechanisms underlying ketamine- and psilocybin-induced symptoms are less well understood.

Recent works suggest that the formation of symptoms induced by psychomimetics could be understood within the framework of predictive coding models (Corlett et al., 2009; Corlett et al., 2011). These suggestions followed from predictive coding models of learning and inference (Friston, 2005b; Rao and Ballard, 1999) and their specific application to schizophrenia (Stephan et al. 2006). Predictive coding assumes a hierarchical neural architecture where each level provides predictions about the state of the level below and evaluates the discrepancy with the actual inputs from the lower level, i.e. prediction error (PE) (Friston, 2005b; Rao and Ballard, 1999). Predictions and PE are conveyed via synaptic connections instantiating a Bayesian message passing scheme. Simply speaking, both perceptual inference and learning rely on minimization of PE throughout the hierarchy. Neuronal states and connection strengths are adjusted during inference and learning, respectively, in order to minimize PE at all levels of the hierarchy.

It has repeatedly been proposed that aberrant PE processing might be involved in the formation of psychosis, originally in the context of associative learning theory (Gray et al., 1991; Hemsley, 1993) and more recently in terms of Bayesian concepts (Fletcher and Frith, 2009; Murray et al., 2008; Stephan et al., 2006). Broadly speaking, these theories constitute two non-exclusive classes which stress either (i) inappropriate timing of PE signals (King et al., 1984; Shaner, 1999); or (ii) inadequate magnitude or precision (inverse variance) of PE estimates during hierarchical Bayesian inference (Corlett *et al*, 2009; Friston, 2005; Stephan *et al,* 2006). These general concepts have been used to explain a range of empirical findings about schizophrenia, such as interpreting fMRI data in terms of a disruption of PE processing in the PFC of schizophrenia patients with delusions (Corlett et al., 2007b)

Critically, the extent of this PE disruption was related to an individual's propensity to delusion formation. Another example is that in the early stage of psychosis, schizophrenia patients often describe how irrelevant stimuli capture their attention (Chapman, 1966). This has been framed in terms of “aberrant salience”, a phenomenological concept originally developed without explicit reference to PEs (Kapur, 2003). More recent proposals (Roiser et al., 2009) have speculated about a link of aberrant salience to contextually irrelevant or “chaotic” PEs (King et al., 1984) which may underlie formation of inappropriate statistical associations, leading to maladaptive inference about the causes of sensory inputs. In summary, abnormal PEs may represent a general mechanism for the emergence of psychotic symptoms in schizophrenia and understanding these symptoms requires formal models that link cognitive impairments to psychopathology.

A commonly used physiological paradigm to estimate PE signaling is the mismatch negativity (MMN) event-related potential (ERP) (Garrido et al., 2009b; Todd and Robinson, 2010), which is most relevant to psychotic symptoms in naturally occurring and drug-induced psychosis (Corlett et al., 2011; Kantrowitz and Javitt, 2010). MMN is an electrophysiological event-related response to unexpected sensory (typically auditory) stimuli, so-called “deviants”, that differ in one physical stimulus dimension from a sequence of preceding identical “standards” (Näätänen et al., 1978). Indeed, deficits in MMN amplitude have been repeatedly reported in schizophrenic patients (Umbricht and Krljes, 2005), and a comparable deficit was found in healthy volunteers after exposure to ketamine (Heekeren et al., 2008; Umbricht et al., 2000). Furthermore, the MMN amplitude assessed under placebo correlated positively with the ketamine-induced positive-like symptoms as indexed by the global score of the Altered State of Consciousness rating scale (5D-ASC) and the BPRS psychosis score in healthy subjects (Umbricht et al., 2002). This correlation was significant over frontal electrodes suggesting that the integrity of PFC is crucial for PE processing in MMN. Another study using a different modality (fMRI) and different paradigm (an associative learning task) suggested that this role of the PFC for PE processing may generalize, reporting that ketamine disrupted PE dependent activity in the right PFC of healthy volunteers (Corlett et al., 2006).

In the current study, we investigated how PE processing is altered under NMDAR antagonist and/or 5-HT_{2A}R agonist manipulation, and whether ketamine- and psilocybin-induced symptoms can be predicted by the MMN. Instead of a classical oddball paradigm, we use a “roving” MMN paradigm and examine the formation and strengthening of memory traces (by quantifying the amplitude of the MMN as a function of the number of preceding standards) (Haenschel et al., 2005; Imada et al., 1993). A notable advantage of the roving paradigm is that physical stimulus differences between standards and deviants are varied independently from the number of standard repetitions in the roving paradigm. This ensures that the ensuing MMN memory trace effect is entirely due to learning and cannot result from differential states of frequency-specific auditory neurons in the temporal cortex.

Materials and Methods

This study was approved by the Ethics Committee of the University Hospital of Psychiatry, Zurich. After receiving a written and oral description of the aim of this study, all participants gave written informed consent statements before inclusion. The use of psychoactive drugs was approved by the Swiss Federal Health Office (BAG), Department of Pharmacology and Narcotics (DPN), Bern, Switzerland.

Subjects

Healthy subjects were recruited at the local university and technical college through advertisement and were then divided into two groups, either receiving (S)-ketamine or psilocybin (ketamine group: N = 19 [male: 12], mean age = 26 ± 5.09 y; psilocybin group: N = 20 [male: 12], mean age = 23 ± 2.27 y).
Prior to the inclusion, subjects' physical health was confirmed by medical history, clinical examination, electrocardiography, and blood analysis. To ascertain the subjects' mental status, all subjects were screened by the DIA-X diagnostic expert system (Wittchen and Pfister, 1997b), a semi-structured psychiatric interview, and the Hopkins Symptom Checklist (SCL-90–R) (Derogatis, 1994b). Furthermore, subjects replied to the Mini-International Neuropsychiatric Interview (M.I.N.I.), a short structured psychiatric interview (Sheehan et al., 1998). We verified the absence of a history of drug dependence or present drug abuse by urine drug-screening and a questionnaire of drug consumption.

Drug administration

In both groups, subjects underwent two sessions (placebo/active drug) in a counterbalanced order. Both subjects and principal investigator were blind to drug order. Subjects stayed monitored and under constant supervision until all drug effects had worn off, and were then released into the custody of a partner or immediate relative.
For the S-ketamine/placebo infusion, an in-dwelling catheter was placed in the antecubital vein of the non-dominant arm. The infusion scheme can be summarized as BET (Krüger-Thiemer, 1968). Once the subject was ready, a bolus injection over 5 min with 10 mg of S-ketamine was given (B). Following one minute break, a continuous infusion with 0.006mg/kg per minute was started (E). To keep S-ketamine levels fairly constant and prevent accumulation in the brain, the dose was reduced by titrating (T). In the placebo session, the same procedure was followed. Instead of S-ketamine, an infusion of physiological sodium chloride solution and 5% glucose was given. Psilocybin was given p.o. at a dose of 115 µg/kg. The specific doses were chosen based on previous studies (Kometer et al., 2011; Vollenweider and Kometer, 2010).

Psychometric assessment of S-ketamine- and psilocybin-induced states (ASC-R)

A revised form of the Altered State of Consciousness (ASC) questionnaire, a visual analogue and self-rating scale, was used to assess the subjective effects of ketamine and psilocybin (Dittrich, 1975; Dittrich, 1998). This revised scale (ASC-R) (Studerus et al., 2010a) comprises three primary dimensions and their respective subscales: (i) “oceanic boundlessness” (OB), referring to positively experienced ego-dissolution associated with changes in the sense of time and emotions, ranging from heightened mood to sublime happiness and feelings of unity with the environment, subsuming the subscales disembodiment, blissful state, spiritual experience, and experience of unity and insightfulness; (ii) “anxious ego-disintegration” (AED), comprising the subscales anxiety and impaired control and cognition including items for disordered thought and loss of control over body and thought; and (iii) visionary restructuralization (VR), including the subscales elementary and complex imagery, audio-visual synesthesias, changed meaning of percepts and auditory alterations.

Auditory test paradigm (mismatch negativity)

Electroencephalograhic (EEG) activity was measured during an auditory “roving” oddball paradigm (Baldeweg et al., 2004; Boly et al., 2011; Garrido et al., 2008a; Haenschel et al., 2005), originally developed by Cowan and colleagues (Cowan et al., 1993b). Acoustic stimuli were generated by E-prime software (Schneider et al., 2002), and applied binaurally through headphones (TDH-39-P, Maico, Minneapolis, MN, USA).

Stimuli comprised a structured train of pure sinusoidal tones, with a roving changing tone (Figure 1). Within each stimulus train, all tones were of one frequency and were followed by a train of a different frequency. The first tone of a train represents the deviant (red), which becomes the standard tone after a few repetitions (blue). Hence, the deviants and standards tones have exactly the same physical properties within one stimulus train, differing only in the number of times they have been presented in the recent past (in a prior stimulus train). The number of times the same tone was presented within one stimulus train varied pseudo-randomly between one and eleven (t = 1-11). The probability that the same tone was presented in one stimulus train (i) was 2.5% for trains with 1 or 2 identical tones, (ii) 3.75% for trains with 3 or 4 identical tones, and (iii) 12.5% for trains with 5-11 identical tones. In other words, 5% of all stimulus trains consisted of 1-2 identical tones, 7.5% of all stimulus trains consisted of 3-4 identical stimuli, and 87.5% of all stimulus trains consisted of 5-11 identical stimuli. The frequency of the tones varied from 500 to 800 Hz in random steps with integer multiples of 50 Hz, tone duration was set at 70 ms, and the inter-stimulus interval was 500 ms.

In parallel, subjects performed a distracting visual task and were instructed to ignore the sounds. It has been argued that the best condition to observe an MMN is when the subject’s attention is directed away from the stimulus (Näätänen, 2000). The task consisted of button-pressing whenever a fixation cross changed its luminance, which occurred pseudo-randomly every 2 to 5 s (not coinciding with auditory changes). The testing session lasted approximately 15 minutes. The purpose of the additional distracting task was to ensure that the participant´s attention was not focused on the tones.

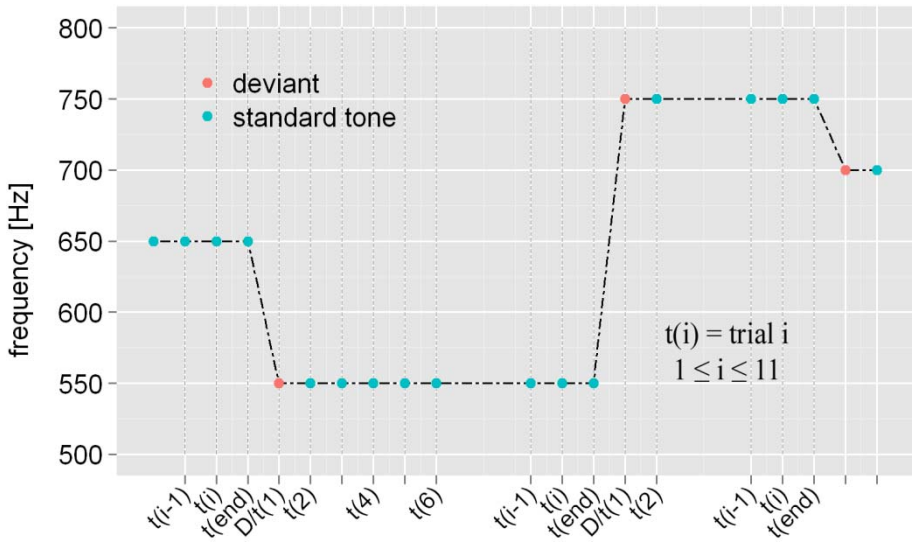

Figure 1 Stimulus design is characterized by a sporadically changing standard stimulus. The first presentation of a novel tone is a deviant (D/t(1); circle) that becomes a standard (triangle), through repetition (t(6)). Standard repetition varied between 1 and 11 (i = 1-11).

EEG/ERP recording

EEG recordings were made from 64 scalp electrodes using the ActiveTwo system (Biosemi, The Netherlands). The horizontal electrooculogram (EOG) was recorded from electrodes attached on the outer canthus of each eye. Similarly, vertical EOG was recorded from electrodes attached infraorbitally and supraorbitally to the left eye. Data were recorded at a sampling rate of 512 Hz. All electrodes were active silver/silver chloride electrodes and were referenced during recording to a common-mode signal (CMS) electrode between POz and PO3 (see http://www.biosemi.com/faq/cms&drl.htm for more details on this setup); the offset of all electrodes was below 25mV, indicating good recording quality.

For ERP analysis, independent component analysis (ICA) was used to remove artifacts due to eye movements and blinks. Following ICA, epochs with a 200-ms prestimulus baseline and a 500-ms poststimulus interval were constructed. Epochs with amplitudes that exceeded ± 100 µV at any electrode were excluded from further averaging. Following artifact rejection, epochs were averaged offline for each subject and were digitally filtered with a band-pass filter (1-30 Hz). MMN was measured as the peak negativity within the 100 to 200 ms window latency of difference waveform (deviant minus standard waveforms). Here, we followed previous studies of the roving paradigm (e.g., (Garrido et al., 2008a) in focusing only on deviants preceded by at least 6 standards. Waveforms were mathematically referenced to an average-mastoid reference prior to peak detection, analogously analyzed as previous studies (Umbricht et al., 2002; Umbricht et al., 2000; Umbricht et al., 2003). Based on previous studies, a set of fronto-central (Fz, F3 and F4) and temporal electrodes (TP7 and TP8) were preselected (Alho et al., 1996; Sato et al., 2000; Tiitinen et al., 1993; Waberski et al., 2001).

Statistical analysis

All statistical analysis was conducted using Statistica 7.1 for Windows (Statsoft Inc., OK, USA). Results of the distracting visual task were evaluated according to signal detection theory (Macmillan, 1991) to determine sensitivity indexes (d') under placebo and following drug administration, which were entered into a repeated-measures analysis of variance (repeated-measures ANOVA) with between-subjects factor *group (ketamine group vs psilocybin group)*. Furthermore, averaged means of MMN difference wave amplitude and latency were subjected to a repeated-measures ANOVA using the within-subjects factors *electrode (frontal vs temporal)*, *treatment* (placebo vs drug) and *standard repetition* (t = 6, 8, 10) and the between-subjects factor *group (ketamine group vs psilocybin group)*. Where the ANOVA null hypothesis of equal means was rejected, we used post-hoc tests (Fisher's least significant difference test, LSD). Additionally, correlations were conducted to examine the effect of the distracting visual task (d' values) on the MMN difference wave amplitudes. Another repeated-measures ANOVA was done to study ketamine- and psilocybin-induced symptoms.
For further analysis, the relative increase of the MMN difference waveform from t(6) to t(8) and further from t(8) to t(10) was computed and the average of these values expressed as "MMN slope". To assess the relationship between MMN slope under "baseline" (drug-free) conditions and drug-induced psychopathology, we correlated (over subjects) the MMN slope under placebo with each symptom rating in the ASC-R questionnaire and Bonferroni-corrected the significance level for multiple testing.

Results

Distracting visual vigilance test

Repeated-measures ANOVA revealed that both drugs produced significantly prolonged reaction times [$F(1,37) = 31.4$, $p < .0000$, $\eta^2 = .46$], as well as reduced sensitivity indices (d') [$F(1,37) = 20.8$, $p < .00001$, $\eta^2 = .36$] (Table 1). Drug effects did not differ from each other, as indicated by the lack of interaction with the between-subjects factor group.

Table 1 Behavioral Results of the Distracting Visual Vigilance Task

	Ketamine group			Psilocybin group		
	Placebo	**Ketamine**	***P*-value**	**Placebo**	**Psilocybin**	***P*-value**
RT (ms)	331 ± 4.3	350 ± 5.2	0.001	340 ± 4.6	360 ± 5.1	0.001
d'	1.9 ± 0.27	1.1 ± 0.22	0.01	1.6 ± 0.28	0.8 ± 0.12	0.01

Mean reaction times (RT) and sensitivity indices (d') ±SE. Both measures were significantly worsened by both drugs, but did not differ significantly between drugs.

MMN memory trace effect (prediction error processing)

A significant main effect for *standard repetition* revealed the systematic increase in MMN amplitude with increasing number of standard tones (memory trace effect) [$F(2,74) = 3.58$, $p < .05$, $\eta^2 = .1$]. In general, both overall MMN amplitude and MMN trace effect were more pronounced over frontal than temporal electrodes ($p < .000001$), as indicated by a significant main effect for *electrode* [$F(1,37) = 145$, $p < .000001$, $\eta^2 = .8$] and a significant *electrode* × *standard repetition* interaction [$F(2,74) = 5.1$, $p < .01$, $\eta^2 = .12$]. Furthermore, a main effect of treatment was found [$F(1,37) = 8.35$, $p < .01$, $\eta^2 = .18$] reflecting an overall attenuation of the MMN amplitude, irrespective of standard repetition, following drug administration. Furthermore, a *treatment* × *electrode* interaction [$F(1,37) = 5$, $p < .05$, $\eta^2 = .12$] revealed that this treatment effect occurred only over frontal electrodes ($p < .00000$). However, the *electrode* × *treatment* × *group* interaction revealed that this treatment effect depended on the location of the electrodes and on the specific drug used [$F(1,37) = 10.5$, $p < .01$, $\eta^2 = .22$]. While psilocybin did not affect the MMN over frontal or temporal electrodes, ketamine did disrupt the MMN but only at frontal electrodes ($p < .00001$) (Figure 2).

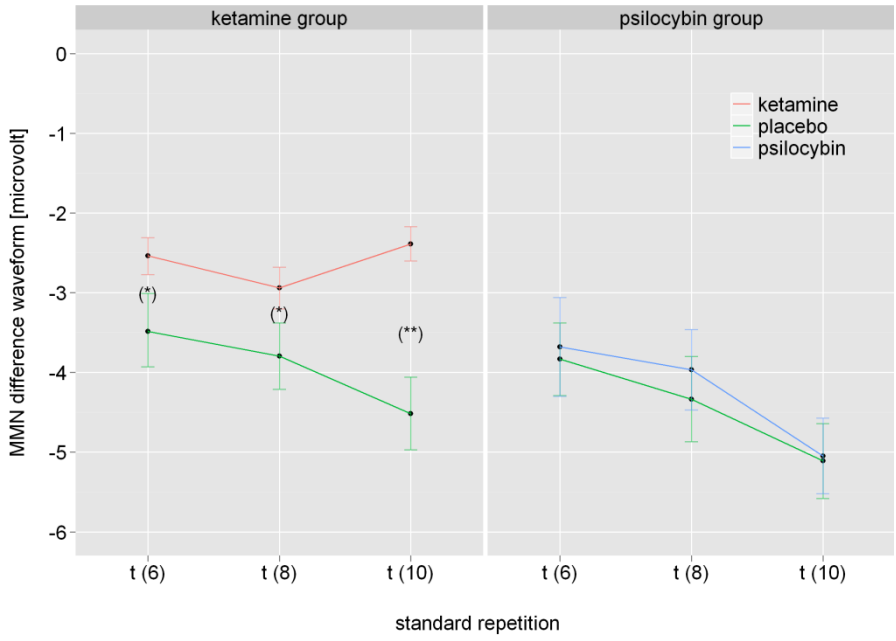

Figure 2 Mean amplitudes ± SE of mismatch negativity (MMN) difference waveforms across standard repetitions (t = 6–10) at frontal electrodes (Fz, F3, and F4) following placebo (green) or drug administration (red: ketamine; blue: psilocybin), respectively. Note: Significant differences between treatment conditions at $^{(*)}$ p at 0.0001 and at $^{(**)}$ p < 0.000001.

A subsequent ANOVA of the ketamine group revealed that ketamine disrupted the MMN memory trace effect over frontal electrodes, indicated by a triple *electrode* × *treatment* × standard repetition interaction [$F(2,36) = 4.7$, $p < .05$, $\eta^2 = .21$]. Post-hoc analysis showed that for the frontal electrodes Fz, F3 and F4 shown in Figure 2 the *treatment* × *standard repetition* interaction was also significant (p at t(6) < .0001; p at t(8) < .0001; p at t(10) < .000001), indicating that the difference in the effect of

ketamine vs. placebo on the MMN trace effect became more pronounced with longer trace length. The corresponding MMN difference waves for the ketamine group were plotted in Figure 3. Finally, as shown by a significant *treatment* × *group* interaction (Figure 3), ketamine but not psilocybin caused a latency shift of the MMN, irrespective of standard repetition [$F(1,37) = 5.29$, $p < .05$, $\eta^2 = .13$].

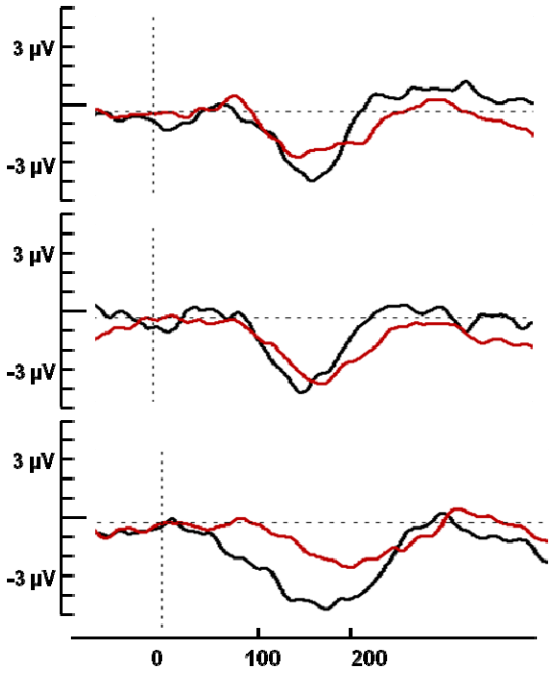

Figure 3 Corresponding mismatch negativity (MMN) difference waveforms following placebo (black line) and ketamine administration (red line) at frontal electrodes (Fz, F3, and F4) for t(6) (above), t(8) (middle), and t(10) (below).

Notably, no significant correlations between the behavioral results of the distracting visual vigilance task (d' values) and the MMN slope in either group were found, suggesting a functional dissociation.

S-ketamine- and psilocybin-induced symptoms (ASC-R questionnaire)

At the dose tested, both ketamine and psilocybin produced similar alterations on the global ASC score that were characterized by derealization and depersonalization phenomena, affective changes, cognitive impairments, and perceptual alterations, reflected by a main effect for *treatment* [$F(1,37) = 69.5$, $p < .000001$, $\eta^2 = .65$]. Subsequent ANOVA with *treatment* and *subscale* as repeated measures and *group* as between-subject factor revealed that both drugs significantly increased all subscale scores (all p's < .01), with the exception of the anxiety score ([$F(11,407) = 4.6$, $p < .00001$, $\eta^2 = .11$]. Additionally, psilocybin-induced auditory alterations were not significantly higher than under placebo. Moreover, post-hoc analysis showed that ketamine produced significantly higher scores than psilocybin for auditory alterations ($p < .05$), for depersonalization as indexed by disembodiment ($p < .000001$) and for cognitive impairments as indexed by impaired control and cognition ($p < .05$) (Figure 4). Otherwise, psilocybin produced more severe elementary imagery ($p < .01$) including visual

illusions and (pseudo-) hallucinations than ketamine. Notably, no correlation was found between drug-induced cognitive impairments (impaired control and cognition) and drug-induced perceptual alterations (auditory and visual). This speaks against the possibility that drug-induced perceptual aberrations induced cognitive impairments.

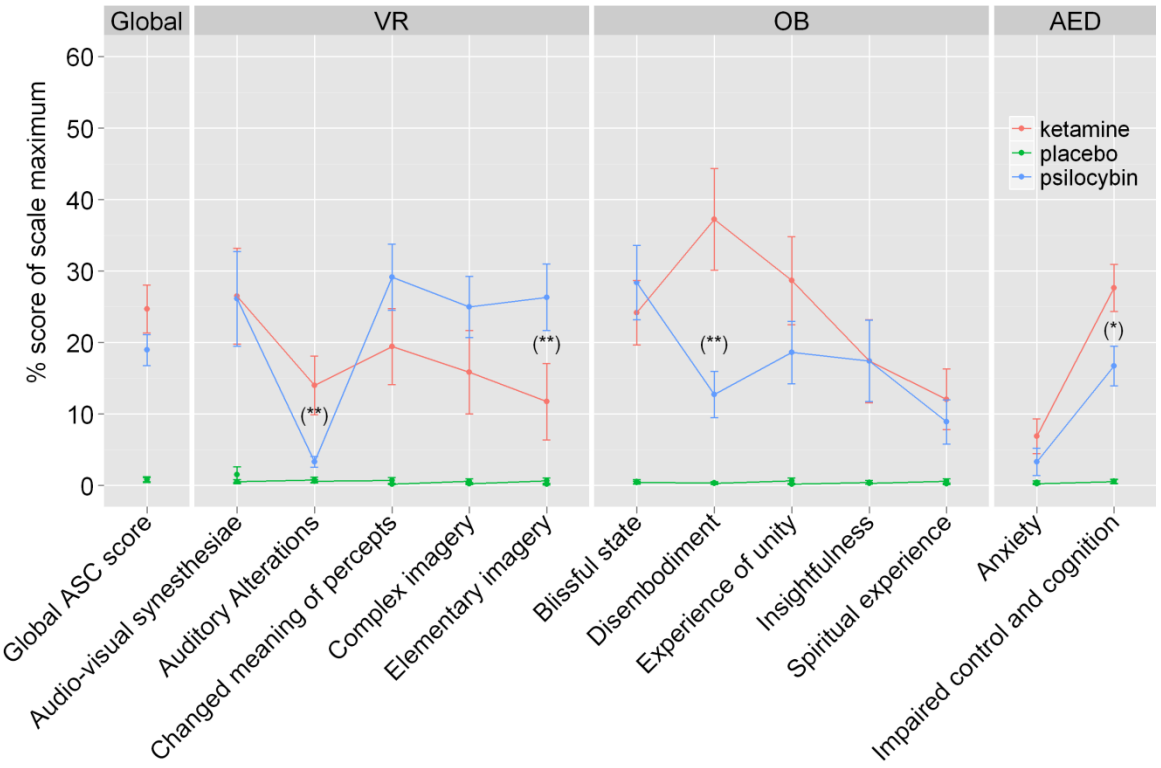

Figure 4 Means ± SE of ketamine- (solid line) and psilocybin-induced (dashed line) symptoms relative to placebo (dotted line) measured with the revised form of the Altered State of Consciousness (ASC-R). Note: Significant differences (least significant difference (LSD) test) between drugs at *p < 0.05 and at **p < 0.01. Symptoms scores were expressed as the percent of scale maximum. The abbreviation VR comprised 'visionary restructuralization', OB means 'oceanic boundlessness', and AED stands for 'anxious ego-disintegration'. Both ketamine and psilocybin increased the global ASC score relative to placebo, but did not differ from each other. Ketamine produced higher score than psilocybin for auditory alterations, disembodiment, and impaired control and cognition. Otherwise, psilocybin produced higher score for elementary imagery than ketamine. No correlation between drug-induced cognitive impairments (impaired control and cognition) and drug-induced perceptual alterations (auditory and visual) was found.

Linking MMN slope and drug-induced symptoms

We assessed the relation between MMN slope under "baseline" (drug-free) conditions at frontal electrodes and drug-induced psychopathology by correlating the MMN slope under placebo with each

symptom rating from the ASC-R questionnaire (under Bonferroni-correction for multiple testing). We found a significant correlation between the MMN slope under placebo and ratings pertaining to *impaired control and cognition* (which includes items for disordered thought and loss of control over body and thought). Critically, this correlation was significant under ketamine ($r = -.67$; $p < 0.05$ Bonferroni-corrected), but not under psilocybin ($r = -.11$; p =ns) (Figure 5). Those subjects who showed the greatest MMN slope under placebo experienced the lowest ketamine-induced cognitive impairments. No other correlations between the MMN slope under placebo and any other drug-induced symptom was found.

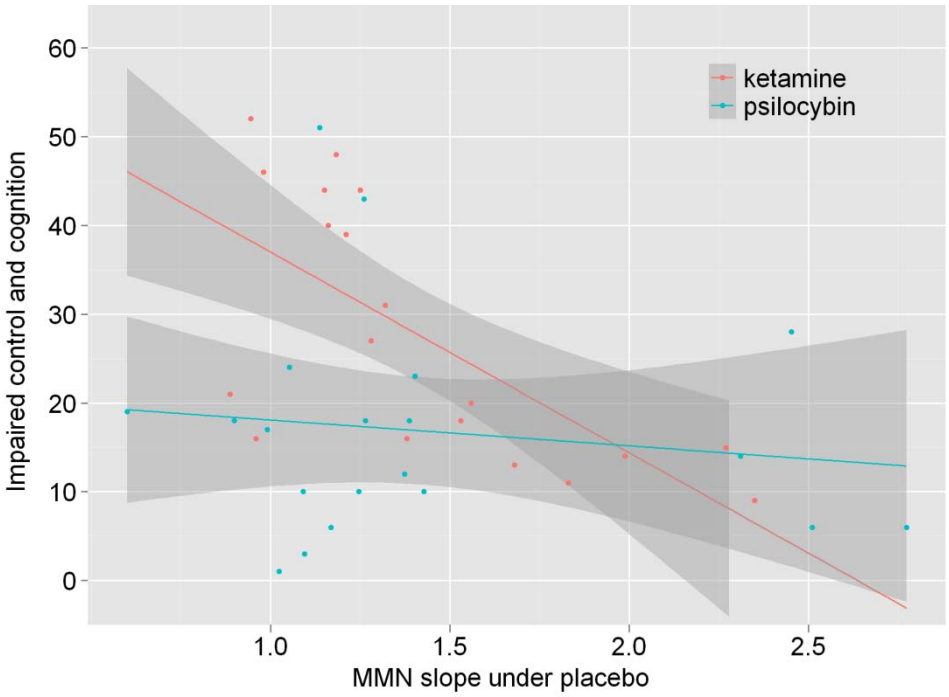

Figure 5 Relationship between the mismatch negativity (MMN) slope under placebo over frontal electrodes and the subscale impaired control and cognition, which includes disordered thought and loss of control over body and thought, induced by ketamine (solid line) and psilocybin (dotted line). Impaired control and cognition scores are expressed as the percentage of the maximum points possible. Notably, the MMN slope under placebo was predictive of ketamine-induced cognitive impairments ($r = - 0.67$; $p < 0.05$), but not of psilocybin-induced cognitive impairments ($r = - 0.11$; p = NS).

Discussion

Our study provides two major results: Firstly, prefrontal PE processing during the roving MMN paradigm is disrupted by the NMDAR antagonist S-ketamine, but not by the 5-HT_{2A}R agonist psilocybin. Secondly, the processing of PE under placebo predicts the severity of ketamine-induced cognitive impairments. In the following, we discuss these findings within a predictive coding framework of MMN (Baldeweg, 2006b; Friston, 2005b; Garrido et al., 2009a; Garrido et al., 2009b), relating them to putative neurobiological mechanisms for the emergence of cognitive impairments.

According to classical theories (Näätänen, 1992), the MMN potential originates from a network comprising the superior temporal gyrus (STG) and the inferior frontal gyrus (IFG) (Garrido et al., 2008a; Opitz et al., 2002b; Rinne et al., 2000c) which detects a disruption within a regularity of preceding standards based on a comparison of the actual sensory input with the already established memory trace (Doeller et al., 2003b; Giard et al., 1990). In this study, we have performed an analysis in sensor space; since EEG sensor signals result from a mixture of neuronal sources, one should be cautious about relating our findings to neural sources in specific locations. In other words, an MMN effect observed at frontal electrodes must not necessarily correspond to a frontal source, and the following discussion should be read with this caveat in mind.
Consistent with other reports using a “roving” oddball design (Baldeweg et al., 2004; Haenschel et al., 2005), a MMN memory trace effect was found in the present study over the frontal cortex; however, no comparable effect was detected over temporal cortical regions. The absence of a temporal MMN memory trace effect suggests that the adaptation hypothesis (Jääskeläinen et al., 2004b), which posits that the MMN results from local neuronal adaptation in the auditory cortex, cannot easily explain the MMN memory trace effect found in the present study. Instead, the frontal MMN memory trace effect may be more plausible understood as a marker of PE caused by the deviation from a learned regularity. This interpretation would be in line with the model adjustment hypothesis (Näätänen and Winkler, 1999; Winkler et al., 1996). However, another roving MMN study in healthy volunteers (which focused on MMN amplitudes in reference to the 6^{th} standard and did not quantify memory trace effects) used dynamic causal modeling and Bayesian model selection to suggest that the model explaining MMN amplitude best was a combination of the adaptation and model adjustment hypotheses. This model accommodates intra-areal adaptation within the STG combined with plasticity of inter-areal connections between temporal and frontal regions (Garrido et al., 2008a). The authors explicitly interpreted their findings within the predictive coding framework, emphasizing that this theory includes both adaptation and model adjustment in the sense that “model adjustment” corresponds to the adjustment of a generative model of future stimuli and “adaptation” corresponds to local changes in post-synaptic gain (Garrido et al., 2008a). Thus, from this perspective, the MMN would arise from a failure to predict bottom-up input and suppress the resulting PE (Garrido et al., 2008a; Garrido et al., 2009b).

As previously reported (Heekeren et al., 2008; Umbricht et al., 2000), the temporal MMN (TP7/TP8) was not significantly altered by S-ketamine in this study, although this lack of effect may have resulted

from the chosen nearby mastoid (TP9/10) reference, which might mask a drug effect on this component. However, similar to the present study, no disruption of the temporal MMN was observed in schizophrenic patients versus healthy controls in two recent studies using the nose as reference and applying a similar "roving" paradigm as used in the present study (Baldeweg et al., 2004; Sato et al., 2003). In contrast to S-ketamine's lack of effect on temporal MMN, our study found that S-ketamine did disrupt the frontal MMN, which is consistent with previous human studies using different MMN paradigms (Heekeren et al., 2008; Umbricht et al., 2000). Here we extend these previous findings by showing that S-ketamine not only reduced the MMN amplitude, but also disrupted the frontally generated MMN memory trace effect compared to placebo. A similar reduction of the frontal memory trace effect was observed in schizophrenic patients (Baldeweg et al., 2004). This finding, together with the established importance of the NMDAR for synaptic plasticity during perceptual learning (Kandel, 2001b; Morris et al., 1986), fits nicely to the role which neurobiologically specific predictive coding theories of MMN have assigned to NMDAR-dependent plasticity. In these theories (Friston, 2005b; Stephan et al., 2006), NMDAR-dependent short-term plasticity is critical for adjusting the strength of glutamatergic synapses connecting hierarchically related cortical areas during perceptual learning. Computationally, this synaptic adjustment is driven by the magnitude of trial-wise PEs in lower-level structures, leading to adjustment of predictions generated by higher-level structures. From this perspective, our finding of a reduced frontal MMN memory trace may reflect the drug-induced perturbation of NMDAR-dependent plasticity of temporo-frontal (forward) connections that serves to adjust PE message passing between the superior temporal gyrus (STG) and the inferior frontal gyrus (IFG) during MMN generation (Garrido et al., 2008a; Opitz et al., 2002b). In other words, the disruption of frontal MMN by S-ketamine may result from a deficient adjustment of prefrontally generated predictions about temporal inputs due to insufficient PE-dependent plasticity of forward connections. We will examine the plausibility of this potential mechanism in future modeling studies. However, the present data cannot fully exclude that increased AMPA receptor conductance following NMDAR blockade (Shi and Zhang, 2003) or downstream effects on the dopaminergic system (Kapur and Seeman, 2001; Vollenweider et al., 2000) may also have contributed to the present findings. Indeed, in the context of predictive coding accounts of psychosis, it was suggested recently that both NMDAR (for backward connections) and AMPAR (for forward connections) contribute to conveying prediction error information (Corlett et al., 2009). In contrast, the empirical data from studies examining the MMN under dopaminergic manipulations indicate that dopamine does not modulate the MMN (Korostenskaja et al., 2008; Leung et al., 2007; Leung et al., 2010).

Some symptoms frequently observed in schizophrenia are not typically interpreted within a Bayesian framework and are usually examined from different perspectives. For example, this include deficits in early information processing as indexed by measures as prepulse inhibition of startle reflex or the P50 auditory evoked potential suppression (Braff et al., 2001; Turetsky et al., 2007). In this context, it has been recently suggested that in schizophrenic patients deficits in early sensory processing may explain the observed reduction in MMN (Leitman et al., 2010). If one accepts S-ketamine as a valid model of schizophrenic symptoms, then this may be seen as a challenge for to our findings. However, given that physical differences between deviant and standard tones were independent of the number

of standard tones in the roving paradigm and that the difference in the effect of ketamine vs. placebo on the MMN trace effect became more pronounced with longer trace length, it seems unlikely that a pure deficit in early sensory processing could account for the ketamine-induced disruption of the MMN memory trace effect. This interpretation is further supported by a lack of correlation between ketamine-induced auditory alterations and the generation of the MMN memory trace effect.

Contrary to S-ketamine, the 5-HT_{2A}R agonist psilocybin neither reduced the MMN amplitude- nor the MMN memory trace effect, which is consistent with a previously reported lack of psilocybin on MMN measured by a classical paradigm (Umbricht et al., 2003). Similarly, a recent MMN study with S-ketamine and the 5-HT_{2A}R agonist DMT showed that the frontal MMN was only affected by S-ketamine and not by DMT (Heekeren et al., 2008). Although 5-HT_{2A}R seems to be involved in different forms of working memory (Williams et al., 2002) and 5-HT_{2A}R agonists such as LSD or DOM enhanced associative learning as measured by eyeblink conditioning in rabbits (Harvey, 2003), the implicit perceptual learning as indexed by the frontal memory trace effect appeared not to be sensitive to manipulations of the 5-HT_{2A}R system (or to the dose of psilocybin used in this study). While, it has been proposed that neuromodulators like serotonin may influence the processing of PE (Corlett et al., 2009) and may be one of the key modulators interacting with NMDARs to produce aberrant synaptic plasticity in schizophrenia (Stephan et al., 2009a), this does not necessarily contradict our findings since such a putative role of serotonin could be expressed in a regionally specific fashion (i.e., in other circuits than the auditory system) and may thus not be a critical factor in PE processing during the MMN paradigm (cf. Garrido *et al,* 2009).

Furthermore, we also explored whether ketamine- or psilocybin-induced symptoms could be predicted by the MMN slope (in the absence of any drug) (i.e., under placebo); in other words, we used two pharmacological models of psychosis to relate individual “baseline” physiology to his/her predisposition to develop psychotic symptoms under pharmacological challenge. This approach is inspired by the general notion that the development of psychiatric disease may result from the interplay between the (genetically determined) susceptibility of an individual and the expose to environmental stressors (Brown, 2011) and follows previous studies which examined whether physiological markers can predict the individual degree of psychotic symptoms in drug-induced psychosis and schizophrenia (Corlett et al., 2006; Honey et al., 2008; Krystal et al., 2003; Umbricht et al., 2002). Here, we found that the MMN slope under placebo showed a negative correlation with the subsequent ketamine-induced extent of cognitive impairments across subjects; in contrast, no comparable relationship was found for psilocybin. While this result is in accordance with Umbricht’s MMN study (Umbricht et al., 2002), it may not appear to be fully consistent with the results by Corlett et al (2006) who found that frontal PE signals under placebo, measured during an associative learning task with fMRI, exhibited a positive correlation with the severity of positive symptoms (delusions, perceptual aberrations) under ketamine. However, the results from the two studies are not directly comparable due to a number of major methodological differences, including different symptom rating scales, different ketamine dosage and application regimes, different measurement techniques (fMRI

vs. EEG) and, perhaps most importantly, fundamentally different cognitive paradigms. Still, one may wonder why individual MMN slope under placebo should predict ketamine-induced cognitive impairments (rather than other symptoms). This can be understood by considering that ketamine disrupts (short- and long-term) NMDAR mediated synaptic plasticity which is a crucial mechanism for PE dependent learning (for review, see Stephan et al. 2006). This is relevant for understanding cognitive impairments or "negative symptoms", such as thought disorder, in schizophrenia because "many, if not all, of them can also be understood as a consequence of aberrant modulation of synaptic plasticity" (Stephan et al., 2009a). In brief, if one is endowed with inadequate PE dependent learning (due to NMDAR related deficiencies) one may be impaired in learning about the statistical structure of the (social and physical) environment and adapting one's beliefs and behavior accordingly. This could explain a wide range of symptoms, from social withdrawal and apathy to thought disorders and aberrant perceptual inference (see Stephan *et al,* 2009 for details). On the other hand, the magnitude of the MMN slope can be seen as expressing the individual capacity for PE dependent learning, i.e., how trial-wise "surprise" about a deviant induces NMDAR dependent short-term plasticity to update predictions about the next trial. In other words, MMN slope may serve as an index of individual capacity of utilizing PEs for adaptive cognition through NMDAR dependent plasticity. From this perspective, one would predict that the higher this individual capacity in the drug-free state (i.e., the higher the MMN slope under placebo), the less pronounced the effects of ketamine on PE dependent learning and subsequent aberrations in adaptive cognition. This is what we found.

To conclude, the present results suggest that the frontal MMN memory trace effect may provide a useful approach to study NMDAR- dependent PE processing during the MMN as a form of implicit perceptual learning. Unraveling the role of NMDAR function in predictive coding may provide valuable insights into pathophysiological mechanisms of schizophrenia in general and the emergence of cognitive impairments in psychosis in particular. This may particularly benefit from a computational modeling approach which uses physiologically interpretable model parameters for clinical predictions (Stephan et al., 2006). In relation to this, recent studies demonstrated that a reduction of MMN can predict the transition of "ultra-high risk" to first-episode psychosis (Bodatsch et al., 2010; Shin et al., 2009). Finally, the assessment of the MMN memory trace effect may also provide a promising tool to assess the efficacy of novel pharmacological treatment, in particular for treatment of cognitive impairments.

Disclosure/Conflict of interest

All authors declare that they have no conflict of interest.

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3. Modeling Ketamine Effects on Synaptic Plasticity During the Mismatch Negativity

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Personal contribution:
AS, MK, KES, and FXV contributed to the study design of this paper. AS and MK developed the MMN roving paradigm. AS contributed to the conduction of the experiments. AS and AOD analyzed the data. AS contributed to the writing of the manuscript, with additional contributions by AOD, MK, KES, KJF and FXV, who appears as co-authors in this paper.

Abstract

This paper presents a model-based investigation of the mechanisms that underlie the well-established reduction of mismatch negativity (MMN) amplitudes under NMDA receptor (NMDAR) antagonists, such as ketamine. We used dynamic causal modeling (DCM) and Bayesian model selection (BMS) to analyze data from a recent study by Schmidt et al. (2011) of event-related responses (ERPs) in healthy volunteers during a roving MMN paradigm, with ketamine applied in a cross-over double-blind placebo-controlled fashion. Our modeling was guided by a predictive coding framework that unifies contemporary “adaptation” and “model adjustment” explanations for the MMN. To this end, we compared a series of alternative dynamic causal models that allowed for different expressions of neuronal adaptation and synaptic plasticity, respectively. Under these models, we obtained three major results. (i) We replicate previous DCM results from non-pharmacological MMN studies that both adaptation and short term plasticity are necessary to explain MMN generation *per se*. (ii) We find significant ketamine effects on synaptic plasticity, but not adaptation, and observe a selective ketamine effect on the forward connection from left primary auditory cortex to left superior temporal gyrus. (iii) This model-based estimate of ketamine effects on synaptic plasticity correlates significantly with ratings of ketamine-induced impairments in cognition and control over subjects. Altogether, although the model employed here represents a simple neural mass formulation and leaves opportunities for future refinement, it suggests a concrete mechanism for ketamine effects on MMN expression that correlates with drug-induced psychopathology. More generally, the present study demonstrates the potential of model-based approaches for inferring on synaptic mechanisms of brain responses, and their pharmacological modulation, from non-invasive EEG data.

Key words: MMN, NMDA receptor, effective connectivity, dynamic causal modeling, DCM, Bayesian model selection, BMS

Introduction

The mismatch negativity (MMN) is an event-related response (ERP) component, measured with electrophysiological techniques such as electroencephalography (EEG) or magnetoencephalography (MEG), observed in response to the violation of a statistical regularity. Operationally, it is defined as the difference waveform obtained by subtracting the ERP to predicted ("standard") stimuli from unpredicted ("deviant") stimuli. While it has been studied most intensively in the auditory domain, it has also been elicited using visual and somatosensory stimuli (Astikainen et al., 2004; Czigler et al., 2004). Ever since its initial description in 1978 (Naatanen et al., 1978), the MMN has played an increasingly important role in cognitive neuroscience. Traditionally, it was seen to reflect a basic process of memory trace formation (Naatanen et al., 2001), which enables automatic, pre-attentive novelty or change detection (Tiitinen et al., 1994; Naatanen, 2000). More recently, the MMN has been interpreted as a electrophysiological index of surprise or prediction error (PE) and treated as a paradigmatic example of perceptual inference and learning within a general hierarchical Bayesian framework of brain function, namely, predictive coding (Rao and Ballard, 1999; Friston, 2005) that can be regarded as an instance of the free energy principle (Friston, 2009).
Beyond cognitive neuroscience and theories of brain function, the MMN has attracted a lot of attention because it is altered in several brain disorders (Naatanen, 2003) with, in particular, significant reductions in schizophrenia patients (Javitt et al., 1998; Baldeweg et al., 2002; Baldeweg et al., 2004; Umbricht and Krljes, 2005; Stephan et al., 2006). The MMN is well-suited as a potential index of pathophysiology because it can be obtained with relatively little effort, and is robust against a number of factors that can confound the interpretation of diagnostically relevant measures from cognitive paradigms, such as attentional state or vigilance (Naatanen et al., 2001). Moreover, the MMN appears to detect the transition of 'ultra-high risk' to first-episode psychosis (Shin et al., 2009; Bodatsch et al., 2010; Atkinson et al., 2011; Orosz et al., 2011), suggesting the potential of the MMN for predicting psychosis risk and progress stages. The clinical utility of the MMN is further established by remarkably consistent findings from neuropharmacological studies, rendering it potentially informative with regard to pathophysiology and treatment: Over the past two decades, numerous pharmacological experiments in animals and humans have indicated that MMN expression can be strongly reduced by antagonizing NMDA receptors (NMDAR) (Javitt et al., 1996; Umbricht et al., 2000; Kreitschmann-Andermahr et al., 2001; Ehrlichman et al., 2008; Heekeren et al., 2008).

Understanding the NDMAR dependence of the MMN is best pursued within a comprehensive theory of the physiological and computational mechanisms that generate MMN responses. One such theory is the so-called *adaptation hypothesis*, which postulates that the MMN arises from adaptation mechanisms in tonotopically organized parts of the auditory system; i.e., neurons in primary auditory cortex that are repeatedly excited by auditory stimuli of the same frequency (May et al., 1999; Jaaskelainen et al., 2004; Ulanovsky et al., 2004). Biophysically, this appeals to mechanisms such as rapid synaptic depression (Zucker and Regehr, 2002) or spike frequency adaptation (Faber and Sah, 2003). An alternative perspective on MMN mechanisms is the *model adjustment hypothesis* which views the MMN as a response reflecting the update of an environmental model that is represented by

a network of temporo-frontal areas and reconfigures in the light of unexpected sensory events (Winkler et al., 1996; Winkler, 2007). Neurophysiologically, this theory speaks to the importance of short-term plasticity of glutamatergic long-range connections between temporal and frontal areas. More recently, a *free-energy theory* of the MMN was formulated that unifies both the adaptation and model adaptation hypothesis and suggests an overarching physiological and computational process that requires both adaptation that is intrinsic to cortical sources and short-term plasticity in extrinsic connections between sources (Garrido et al., 2008; Garrido et al., 2009b; Garrido et al., 2009a). This theory interprets the MMN as a prediction error signal (generated by pyramidal neurons in supragranular layers) during predictive coding in the auditory processing hierarchy, where each level attempts to minimize the discrepancy between bottom-up inputs from the level below and top-down predictions from the level above. By recurrent message passing across levels and prediction error-dependent synaptic plasticity, this circuit achieves minimizes free-energy (an approximation to the information theoretic measure of surprise) across the entire hierarchy, enabling inference about the causes of sensory input and optimal learning about statistical regularities (Friston, 2009). Importantly, the free-energy theory of the MMN incorporates the two key physiological mechanisms implied by the two previous theories: local adaptation and short-term plasticity of inter-regional glutamatergic synaptic connections. The former controls the post-synaptic gain of neurons encoding prediction error (such that inputs with low precision or high uncertainty have less impact on predictions), while the latter optimizes inter-regional synaptic weights during learning and thus regulates the transmission of predictions and their errors across the hierarchy.

While the free energy principle is a very generic theory of brain function (Friston, 2010), it has been particularly useful for framing studies of MMN mechanisms. Of particular relevance for the present study is that both of the key processes described above – adaptation and short-term plasticity of glutamatergic connections – are regulated by NMDARs. The free energy formulation thus offers an opportunity to address the question, from a model-based perspective, which synaptic mechanism may underlie the empirically well-established NMDAR-mediated reduction of the MMN. It is conceivable that this effect could be expressed entirely at the level of neuronal adaptation because spike frequency adaptation results from potassium channel dependent hyperpolarization which, in turn, relies on intracellular calcium influx that is modulated by NMDAR status (Faber and Sah, 2003). On the other hand, it is equally conceivable that the NMDAR-mediated MMN reduction results from aberrant short-term plasticity of inter-regional glutamatergic connections. This is because activation of NMDARs can lead to rapid changes in the strength of glutamatergic synapses, e.g. via phosphorylation of AMPA receptors (AMPARs) (Wang et al., 2005). A third option is that both mechanisms contribute to empirically observed NMDAR effects on MMN expression.

Clearly, these competing accounts cannot be disentangled by traditional ERP analyses that rely on simple subtraction of evoked responses. Instead, we need to evaluate the relative plausibility of different physiologically interpretable models that can be fitted to empirically measured MMN responses. This allows us to assess the relative contributions from adaptation and short-term plasticity of glutamatergic connections, and how they change under NMDAR antagonists. A general framework for model-based assessment of competing theories about neuronal circuits is dynamic causal

modelling (DCM; (Friston et al., 2003; Stephan et al., 2010)). DCM is a generic Bayesian system identification technique that has gained popularity in neuroimaging and electrophysiology over the past few years and allows for inference on “hidden” neurophysiological mechanisms that generated observed measures, such as blood oxygen level dependent (BOLD) signal in fMRI or evoked responses measured with EEG. The key idea here is to formulate a simplified model of neuronal population responses and combine this with a modality-specific forward model such that one can predict the measurement that would arise from any particular neuronal circuit. Given such a generative model and known experimental perturbations (stimuli), one can invert the model and thereby compute the posterior probability of the model parameters, given the data. Furthermore, alternative models embodying competing hypotheses about the mechanisms generating the data can be evaluated using their model evidence, a principled measure of the balance between model fit and model complexity (Penny et al., 2004). While DCM has been formulated for different modalities (cf. (Kiebel et al., 2009; Stephan et al., 2007)), its current implementation for ERPs represents a neural mass formulation of interacting cortical sources (David et al., 2006), with distinct representations of adaptation and synaptic plasticity that have proven very useful in previous MMN studies (Kiebel et al., 2007a; Garrido et al., 2008; Garrido et al., 2009b). In this paper, we use this implementation of DCM for inferring on the physiological mechanisms that underlie empirically measured reductions of MMN amplitude under the influence of the NMDAR antagonist ketamine. The data analyzed here were from a recent study by Schmidt et al. (2011) who examined 19 healthy volunteers with a roving MMN paradigm (Haenschel et al., 2005; Garrido et al., 2008) on two sessions, using a cross-over double-blind placebo-controlled design. As previously reported, the ERP analyses of these data indicated a significant reduction of the MMN at fronto-central electrodes following ketamine administration (Schmidt et al., 2011), which is consistent with a number of previously published reports in humans and animals, using conventional (non-roving) MMN paradigms (Javitt et al., 1996; Umbricht et al., 2000; Umbricht et al., 2002; Heekeren et al., 2008).

In this paper, we apply DCM and BMS to the data from Schmidt et al. (2011) to address the following three questions. First, can we replicate the results of previous (non-pharmacological) DCM studies of the MMN that evaluated a set of competing models inspired by the free energy formulation (Garrido et al., 2008; Garrido et al., 2009b)? Secondly, which of the two mechanisms of interest - intrinsic adaptation or extrinsic short-term glutamatergic plasticity - contributes most to explaining ketamine effects on MMN expression, and are these mechanisms regionally specific? Finally, can we validate our model-based approach by finding a correlation between model parameter estimates and cognitive measures altered by ketamine?

In brief, (i) we replicate previous DCM results from non-pharmacological MMN studies that both adaptation and short term plasticity are necessary to explain MMN expression *per se*, (ii) we find significant ketamine effects on synaptic plasticity, but not adaptation, and observe a selective ketamine effect on forward connections from left primary auditory cortex, and finally, (iii) we observe a significant correlation between ketamine-induced changes in plasticity of auditory forward connections and introspective measures of cognition.

Methods

The participants, drug administration and data acquisition have previously been described in Schmidt et al. (2011) and the interested reader is referred to this paper for details. Here, we summarize the most important aspects and provide details of data analysis with DCM and BMS.

Subjects

This study was approved by the Ethics Committee of the University Hospital of Psychiatry, Zurich. After receiving written and oral descriptions of the aim of the study, all participants gave written informed consent statements before inclusion in the study. The use of psychoactive drugs was approved by the Swiss Federal Health Office (BAG), Department of Pharmacology and Narcotics (DPN), Bern, Switzerland.

Healthy subjects were recruited at the local university and technical college through advertisement (N = 19; male: 12, mean age = 26 ± 5.09 years). The study of Schmidt et al. (2011) also included a group of subjects receiving psilocybin vs. placebo. As no effect of psilocybin on the MMN was found, this group was not included in the present study.

Prior to inclusion, the subjects' physical health was confirmed by medical history, clinical examination, electrocardiography, and blood analysis. To ascertain the subjects' mental status, all subjects were screened by the diagnostic expert system (Wittchen and Pfister, 1997), a semi-structured psychiatric interview, and the Hopkins Symptom Checklist (SCL-90–R) (Derogatis, 1994). Furthermore, subjects also underwent the Mini-International Neuropsychiatric Interview (M.I.N.I.), a short structured psychiatric interview (Sheehan et al., 1998). We verified the absence of a history of drug dependence or present drug abuse by urine drug-screening and a questionnaire that assessed previous drug consumption.

Drug Administration and Psychometric Assessment of S-ketamine State

Subjects underwent two sessions (placebo and S-ketamine) in a counterbalanced fashion at an interval of at least 2 weeks. Both subjects and the principal investigator were blind to drug order. Subjects were monitored and under constant supervision until all drug effects had worn off, and were then released into the custody of a partner or immediate relative. For the S-ketamine/placebo infusion, an in-dwelling catheter was placed in the antecubital vein of the non-dominant arm. Once the subject was ready, a bolus injection of 10 mg over 5 min was delivered. Following 1 min break, a continuous infusion with 0.006mg/kg per min was administered over 80 minutes. To keep S-ketamine's plasma level fairly constant, the dose was reduced every ten minutes by 10% (Feng et al., 1995; Vollenweider et al., 1997). In the placebo session, the same procedure was followed and an infusion of physiological sodium chloride solution and 5% glucose was administered.

The Altered State of Consciousness (ASC) questionnaire, a visual analogue and self-rating scale, was used to assess the subjective effects of S-ketamine (Dittrich, 1975; Dittrich, 1998). A recent evaluation

study of the ASC questionnaires has constructed eleven new lower order scales (Studerus et al., 2010), which were analyzed in this study.

Experimental Design

Electroencephalographic (EEG) activity was recorded during an auditory "roving" oddball paradigm, originally developed by Cowan and colleagues (Cowan et al., 1993) and subsequently modified by Baldeweg et al. (2004), to assess the mismatch negativity (MMN) response. Acoustic stimuli were generated using the E-prime software (Schneider et al., 2002), and were presented binaurally through headphones (TDH-39-P, Maico, Minneapolis, MN, USA).

The stimuli consisted of seamlessly connected trains of pure sinusoidal tones with a roving frequency structure. Within each stimulus train, all tones were of one frequency and were followed by a train of tones of a different frequency. The first tone of a train represented the deviant, which became a standard tone after a few repetitions. Therefore, the deviant and standard tones had exactly the same physical properties within one stimulus train, differing only in the number of times they had been presented in the recent past. The number of times the same tone was presented within one stimulus train varied pseudo-randomly between one and eleven (t = 1-11). The probability that the same tone was presented in one stimulus train was (i) 2.5% for trains with 1 or 2 identical tones, (ii) 3.75% for trains with 3 or 4 identical tones, and (iii) 12.5% for trains with 5-11 identical tones. In other words, 5% of all stimulus trains consisted of 1-2 identical tones, 7.5% of all stimulus trains consisted of 3-4 identical stimuli, and 87.5% of all stimulus trains consisted of 5-11 identical stimuli. The frequency of the tones varied from 500 to 800 Hz in random steps with integer multiples of 50 Hz, tone duration was set at 70 ms, and the inter-stimulus interval was 500 ms.

In parallel, subjects performed a distracting visual task and were instructed to ignore the sounds. This follows the suggestion that MMN assessment is optimal when the subject's attention is directed away from the auditory domain (Naatanen, 2000). The task consisted of button-press responses whenever a fixation cross changed its luminance, which occurred pseudo-randomly every 2 to 5 s (not coinciding with auditory changes). The experimental session lasted approximately 15 minutes.

Data Acquisition and Preprocessing

The EEG was recorded at a sampling rate of 512 Hz using a Biosemi system with 64 scalp electrodes. The horizontal electro-occulogram (EOG) was recorded from electrodes attached on the outer canthus of each eye. Similarly, the vertical EOG was recorded from electrodes attached infraorbitally and supraorbitally to the left eye.

Pre-processing and data analysis was performed using SPM8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/). Continuous EEG recordings were referenced to the average, down-sampled to 300Hz, and bandpass filtered between 0.5 and 30Hz. The data were then epoched into 500ms segments using a peri-stimulus window of 100ms. For each subject and in each condition, two trial types were defined, the deviant trial (first tone within a new train) and a standard trial (operationally defined as the sixth tone, as in Garrido et al. 2008). The artefact rejection procedure

used a thresholding approach to detect problematic trials or channels. Trials in which the signal recorded at any of the channels exceeded 80 microvolts relative to the pre-stimulus baseline were removed from subsequent analysis. Most of the artefacts that were detected reflected vertical and horizontal eye-movements, which were monitored using ocular electrodes. The average number of artefact-free trials was 124 and 172 for standard and deviant trials in the placebo condition, and 153 and 207 for standard and deviant trials in the ketamine condition. Grand averages were computed using robust averaging, a weighted least squares procedure which incorporates a weighting matrix into the estimation so that outlier values exhibit less influence on the overall mean (Wager et al., 2005).
The data were subject to standard analyses using statistical parametric mapping (SPM) – over channels and peristimulus time – to establish condition (standard versus oddball) effects and any interaction with ketamine at the between subject level. The same data were then subject to dynamical causal modelling in an attempt to explain the differences observed in terms of adaptation and changes in extrinsic connectivity. For the SPM analyses, the averaged data from each trial type and each condition were converted to scalp images for all 64 channels and 151 time points using a voxel size of 4.25mm x 5.38mm x 3.33mm. The images were constructed using linear interpolation for (removed) bad channels and smoothing to accommodate for between-subject spatial and temporal variability in channel space. Dynamic causal modelling was applied to the preprocessed channel data to explain observed responses in source states. For computational expediency, all dynamic causal models (see below) were computed on a reduced channel space that corresponded to eight channel mixtures or spatial modes. The eight spatial modes were calculated using singular value decomposition (SVD) of the channel data over a temporal window of interest. Following Garrido et al. (2008), the temporal window of interest was confined to 0-250ms post-stimulus to ensure selective modelling of the MMN response (as opposed to later components).

Dynamic Causal Modelling

Neurophysiologically plausible forward models are essential for understanding how event-related potentials (ERPs) are generated. One such approach is dynamic causal modelling (DCM) which was originally developed for connectivity analysis of fMRI data (Kiebel et al., 2007b) and was subsequently implemented for a range of other data modalities and features, such as ERPs measured by EEG (David et al., 2006). DCM uses a biologically informed causal model to make inferences about the underlying neural mechanisms that generate observed event-related responses. This approach provides an important advance over conventional source reconstruction techniques for ERP data because it places neurobiological constraints on the model inversion, in which the parameters of the reconstruction have a specific neuronal interpretation. These parameters describe, for example, the synaptic coupling strength among sources and post-synaptic gain, and how these properties depend upon stimulus attributes or experimental manipulations (David et al., 2006; Kiebel et al., 2006).
The implementation of DCM for ERPs in SPM8 uses a neural mass model of cortical source (Jansen and Rit, 1995) that contains interacting inhibitory and excitatory subpopulations of neurons. Specifically, each source is described in terms of the average post-membrane potentials and firing rates of three neuronal subpopulations of pyramidal cells, spiny-stellate cells and inhibitory

interneurons. The cortical sources are linked by forward, lateral and backward connections (Linn et al., 1999) and conform to a hierarchical model of intrinsic and extrinsic connections within and between multiple sources as described in previous studies (David et al., 2005; Nee et al., 2007).
In order to estimate the model parameters that best explain how the observed data were generated, DCM inverts a spatio-temporal model covering all sensors or spatial modes and the temporal window of interest. The neural parameters describe synaptic connectivity strengths, post-synaptic gain, propagation delays among sources and various synaptic rate constants. The spatial parameters, on the other hand, specify the location and orientation of equivalent current dipoles. We used a four concentric sphere head model with homogenous and isotropic conductivity as an approximation to the brain, the cerebrospinal fluid (CSF), skull and scalp surfaces. We specified an equivalent current dipole (ECD) model with uninformed priors about the dipole orientations and informed priors about the source locations (Penny, 2011), using the same coordinates as Garrido et al. (2008) for defining prior surface location means with a prior variance of 16 mm^2. The moment (orientation) parameters had prior means of zero and a variance of 256 mm^2 in each direction, which is equivalent to assuming uninformed priors on the orientations of the dipoles.
Bayesian inversion of the combined neuronal and spatial model provides a posterior distribution for each parameter whose variance represents the uncertainty about the parameter after observing the data. Furthermore, the uncertainty about the model itself is addressed using Bayesian model comparison based on an approximation to the model evidence. These procedures are explained in detail elsewhere (Penny et al. 2004; Stephan et al. 2009) and are briefly summarized below.

Model specification

DCM is a hypothesis driven method that does not explore all possible models, but tests a specified model space based on prior knowledge about the system of interest. The network architectures that we tested in the present study were motivated by the results of previous MMN examinations (Doeller et al., 2003; Garrido et al., 2008; Grau et al., 2007; Opitz et al., 2002; Rinne et al., 2000). These studies suggest that the main cortical generators of the MMN include bilateral primary auditory cortex (A1), bilateral superior temporal gyrus (STG) and the right inferior frontal gyrus (IFG). The coordinates used for specification of our ECD model were informed by the above studies and identical to the ones previously used by Garrido et al. (2008) in the original DCM examination of the roving MMN.
In this study, we compared 8 distinct models that might underlie the generation of MMN in response to a deviant tone. These models were created by systematic combinations of the two key mechanisms proposed by predictive coding schemes under the free-energy principle. The first mechanism was short-term plasticity of glutamatergic long-range connections. In DCMs of the MMN, this is typically modeled by allowing for a modulation of the synaptic coupling strength of inter-regional forward and backward connections when the deviant tone is presented (cf. (Garrido et al., 2008; Garrido et al., 2007). The corresponding DCM parameters express (as a multiplicative factor or scaling coefficient) the coupling change relative to the standard tone. We allowed for different expression of this type of plasticity, creating four models: no modulation of connections by the deviant tone (model 1), modulation of either forward or backward connections among A1, STG, and IFG (models 2 and 3), and

modulation of both forward and backward connections among the three brain regions (model 4). With these four models, we hypothesized that the differences between the deviant and the standard are caused by short-term plasticity of connections within the temporofrontal network, representing the reconfiguration of this network in response to prediction error or surprise (cf. *model adjustment*).
The second mechanism represented by our models concerned neuronal adaptation. That is, in models 5 through 8 we repeated the same variations in synaptic plasticity as for the first 4 models, but additionally we allowed for variations in adaptation, expressed in terms of deviant-induced modulation of the post-synaptic gain (responsiveness or excitability) in left and right A1 (see Figure 7a). This addressed the *adaptation hypothesis*, which postulates that the MMN arises predominantly from post-synaptic mechanisms such as spike-frequency adaptation as result of an increase in calcium-dependent potassium conductance (May et al., 1999; Ulanovsky et al., 2004). In DCMs of the MMN, a lumped representation of adaptation mechanisms can be achieved by allowing for a modulation of post-synaptic gain parameters (this has previously also been referred to as modulation of "intrinsic connections"; (Kiebel et al., 2007a). Thus, models 5 through 8 examine the hypothesis of both fronto-temporal interactions and local adaptation within A1 as the neural mechanisms underlying the generation of the MMN response.
Overall, the 8 models tested here are similar, but not identical, to the 6 models considered by Garrido et al. (2008). We used the same type of DCM, time window (0-250ms), number of spatial modes and dimensions of model space (i.e., adaptation and synaptic plasticity). In addition to Garrido et al. (2008), however, we also tested models without synaptic plasticity anywhere in the network (models 1 and 5; Figure 7a) and introduced additional inter-hemispheric connections between A1 and STG, respectively, in both hemispheres (Figure 7a).

Statistical analysis

The statistical analyses employed in this paper were based on the standard two-stage (summary statistics) approach in DCM, i.e., model selection followed by interrogation of posterior estimates (Stephan et al., 2010). In the first stage, Bayesian model selection (BMS) was used to determine the optimal network architecture underlying electrophysiological responses to auditory stimulation. In a second stage, posterior parameter estimates were examined to detect differences between placebo and ketamine conditions. This second stage used the posterior means averaged over the DCMs of each subject (Bayesian model averaging, BMA) as the dependent variables for a multivariate Hotelling's T^2 test and subsequent univariate t-tests (see below for details).

Bayesian Model Selection and Bayesian Model Averaging

From a Bayesian perspective, alternative models that represent competing hypotheses about the mechanisms generating observed data are evaluated by comparing their (log) evidence. The log-evidence corresponds to negative surprise about the data or the (log) probability of the data given a model. It represents a principled measure, derived from probability theory, of the balance between model fit and model complexity. Since it cannot be computed analytically except for linear Gaussian

models, approximations to the log-evidence are usually required. The approximation used here is the (negative) free energy that provides a bound-approximation on the log evidence and can be obtained using Variational Bayes (VB) (Friston et al., 2007).

The evidence can be decomposed into two components: the accuracy term, which quantifies the data fit, and a complexity term which penalizes models with many degrees of freedom (e.g., many and/or uninformed parameters). The best model given the data is the one with the largest log model evidence, ln $p(y|m)$ (assuming a uniform prior over all models). Models can be compared by computing evidence ratios (Bayes factors) or log evidence differences. Following conventional classifications (Kass and Raftery, 1995)), one concludes that there is strong evidence in favour of a model if the difference in log evidence is greater than 3 compared to another model (i.e., a Bayes factor of 20).

Furthermore, inference about general characteristics of model architecture can be obtained by using family-based inference, which compares sets of models grouped by architectural properties (Heresco-Levy et al., 2007). In the present study we used family level inference to determine whether modulation of post-synaptic gain in bilateral A1 constituted an important addition to the model architecture. Thus, we specified two model families, the first without and the second with post-synaptic gain modulation present at the level of bilateral A1. We performed family-wise inference, using a random effects approach, which is robust to potential outliers in the population (Stephan et al., 2009b). Prior to the subsequent analysis of differences in posterior parameter estimates across drug conditions, we used Bayesian model averaging (BMA) (Penny et al., 2010) which averages over models, weighted by the posterior model probabilities. In this way, BMA provides parameter estimates that account for model uncertainty.

Analysis of Model Parameter Estimates

Following BMA, we used the resulting posterior means from the averaged DCMs for examining differences in deviant-induced changes in adaptation (post-synaptic gain) and synaptic plasticity (parameterized in terms of condition dependent coupling changes) between placebo and ketamine conditions. First, we used a multivariate Hotelling's T^2 test, testing whether the two sets of parameter estimates encoding neuronal adaptation and short-term synaptic plasticity, respectively, were significantly different between ketamine and placebo conditions. This drug-induced difference was significant for the parameters representing synaptic plasticity, but not for neuronal adaptation. Based on this result we used, in a second step, univariate post-hoc t-tests, asking which of the six forward and backward connections in the model contributed individually to explaining the ketamine effects. We Bonferroni-corrected the results for the number of parameters tested. Finally, in a third step, we used a simple regression analysis to examine the relationship between the model parameters showing significant changes under ketamine and the independent ratings on the ASC questionnaire after ketamine administration.

Results

MMN responses due to repetition effects

A conventional analysis of MMN amplitudes and latencies from this group of subjects has been presented by Schmidt et al. (2011). Here, we complement these analyses by a spatiotemporal characterization of the MMN response using statistical parametric mapping (in sensor space) and whole-brain correction for multiple tests (family-wise error correction using Gaussian random field theory as implemented in SPM8). The goal of this initial analysis was to verify the presence of a MMN response for each subject and each condition, prior to subsequent modeling. Two out of 19 subjects failed to show a significant MMN response in both placebo and ketamine conditions, and were therefore excluded from subsequent DCM analyses. In the placebo condition, the MMN response was observed over frontal and central electrodes between 110 and 220 ms. Figure 1 illustrates the grand mean responses averaged across all subjects in the placebo condition, comparing responses to "deviant" trials (first tone within stimulus trains, dashed lines) with responses to "standard" trials (sixth tone, solid black lines).

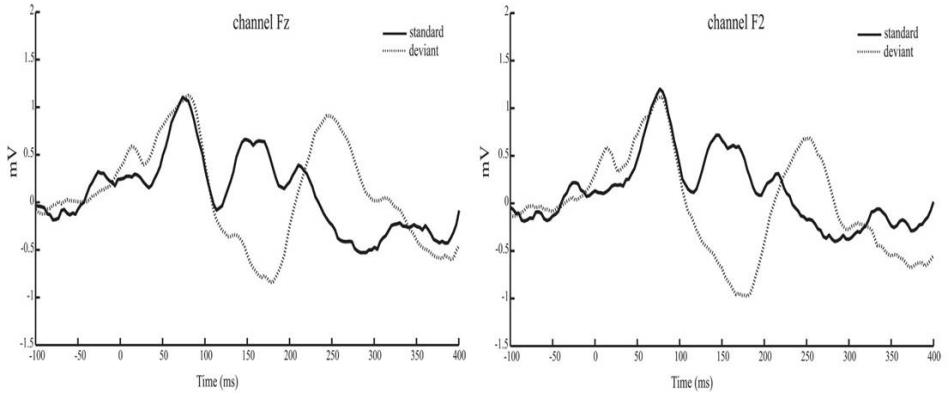

Figure 1 Grand average ERP responses in the placebo condition to the sixth tone of stimulus trains ("standard tone"; black line) and the first tone of stimulus trains ("deviant" tone; dashed line) across frontal and central electrodes.

The MMN response peaked at 177ms from tone onset, which is consistent with previous studies (c.f.,(Cowan et al., 1993; Fletcher and Frith, 2009; Garrido et al., 2008). Figure 2 shows a 3D spatiotemporal characterization of the MMN response using statistical parametric mapping to compare the deviant to the standard tones in the placebo condition. The analysis was performed across the entire epoch [-100 400] and over all 64 channels. As noted above, for these analyses the scalp topography at any time-bin was interpolated from 64 channels and smoothed. Figure 2 shows the statistical parametric map (SPM) where, over subjects, there is a significant negative amplitude deflection as a result of the deviant tone [$t(32) = 5.26$, $p < 0.05$, family-wise error corrected]. This result suggested a significant MMN response over bilateral frontal channels between 160 and 180ms with maximum at 180 ms.

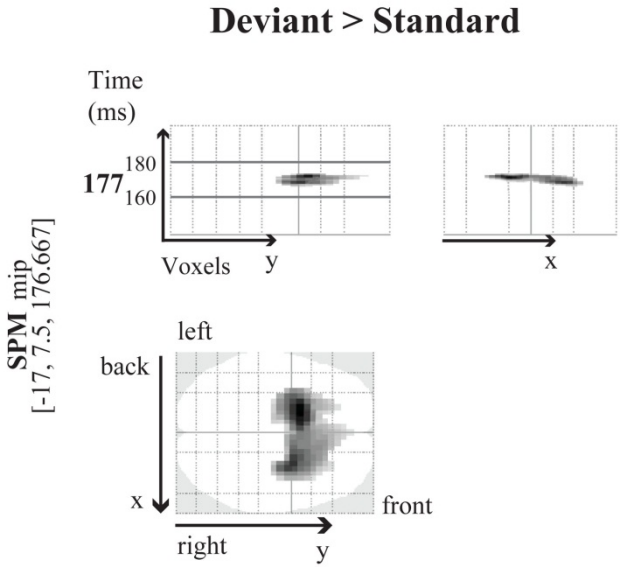

Figure 2 Spatiotemporal representation of the MMN response in the placebo condition: comparison between the first and the sixth tone presentations, the “deviant” and the “standard”, respectively. SPM analysis was performed across all 64 channels and across the entire epoch [-100 400]. The SPM results show a significant negative difference over bilateral frontal electrodes in the range of 160 and 180 ms, peaking at 177 ms.

In the ketamine condition, we also observed a MMN response over frontal and central electrodes between 110 and 220 ms. Figure 3 shows the grand mean responses across all subjects in the ketamine condition in response to the deviant tone (dashed lines) compared to the standard tone (grey).

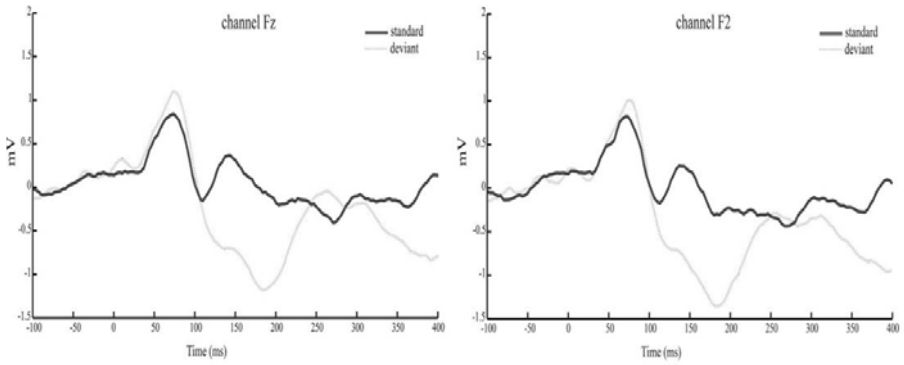

Figure 3 Grand average ERP responses in the ketamine condition to the sixth tone of stimulus trains (“standard tone”; black line) and the first tone of stimulus trains (“deviant” tone; dashed line) across frontal and central electrodes.

In the ketamine condition, the MMN response was also seen in right frontal channels between 140 and 160ms with a maximum at 150ms [t (32) = 5.25, p < 0.05 FWE]. A late response was observed on the ketamine as well, peaking at 390ms in central electrodes.

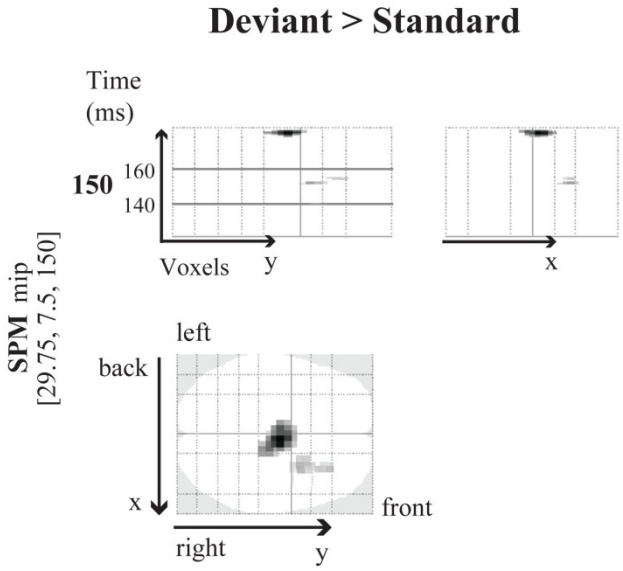

Figure 4 Spatiotemporal representation of the MMN response in the ketamine condition: comparison between the first and the sixth tone presentations, the "deviant" and the "standard", respectively. SPM analysis was performed across all 64 channels and across the entire epoch [-100 400]. Similarly to the placebo group, the SPM results show a significant negative difference over right frontal electrodes in the range of 140 and 160 ms, peaking at 150 ms.

Importantly and in accordance with previous studies, the MMN response was significantly attenuated in the ketamine compared to the placebo condition. Figure 5 illustrates the difference waveform, which contrasts the deviant tone to the standard tone, in placebo and ketamine conditions. In the placebo condition, the MMN response was larger over frontal and central electrodes between 150 and 180ms and between 220 and 300ms.

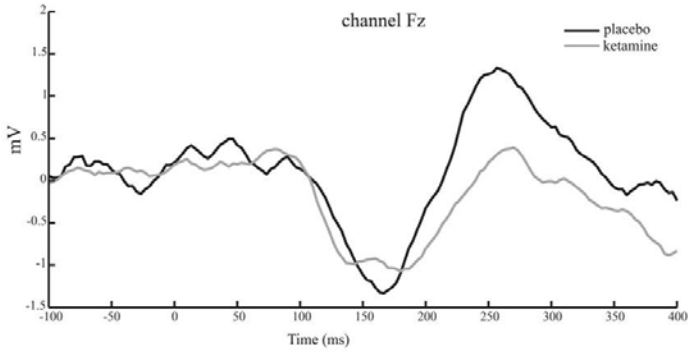

Figure 5 Grand average difference waveform in placebo (black line) and S-ketamine (grey line) conditions across frontal and central electrodes.

A paired SPM t-test was performed in order to compare the MMN (differences between standard and oddball tones) between placebo and ketamine conditions. Significant differences between the MMN under placebo and ketamine conditions were observed [t (16) = 3.68, p < 0.05 corrected for a search volume defined by the main effect of MMN] in fronto-central and central electrodes between 220 and 240ms with a maximum at 230ms. See Figure 6. These results confirm that the MMN response was significantly larger in the placebo compared to the ketamine condition.

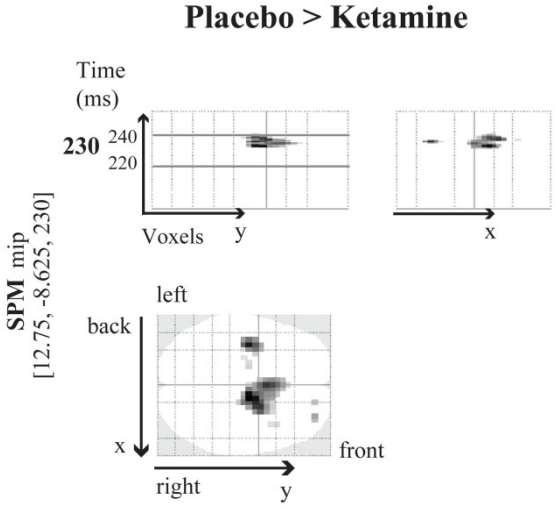

Figure 6 Spatiotemporal representation of the effect of S-ketamine administration: comparison between placebo and S-ketamine conditions. SPM analysis was performed across all 64 channels and across the entire epoch [-100 400]. The SPM results show a significantly larger MMN response in the placebo condition compared to the S-ketamine condition over frontal and central electrodes in the range of 220 and 240 ms, peaking at 230 ms.

DCMs of the MMN response

As described in the Methods section, we defined a space of 8 models systematically combining mechanisms of adaptation in A1 with synaptic plasticity expressed by different extrinsic connections of our temporo-frontal network. Random effects BMS indicated that the model with plasticity in forward and backward connections as well as adaptation (expressed via post-synaptic gain modulation in A1) had the largest model evidence and was clearly superior to all other models at the group level (exceedance probabilities >80% for placebo and >70% for ketamine; see Fig. 7a-c).

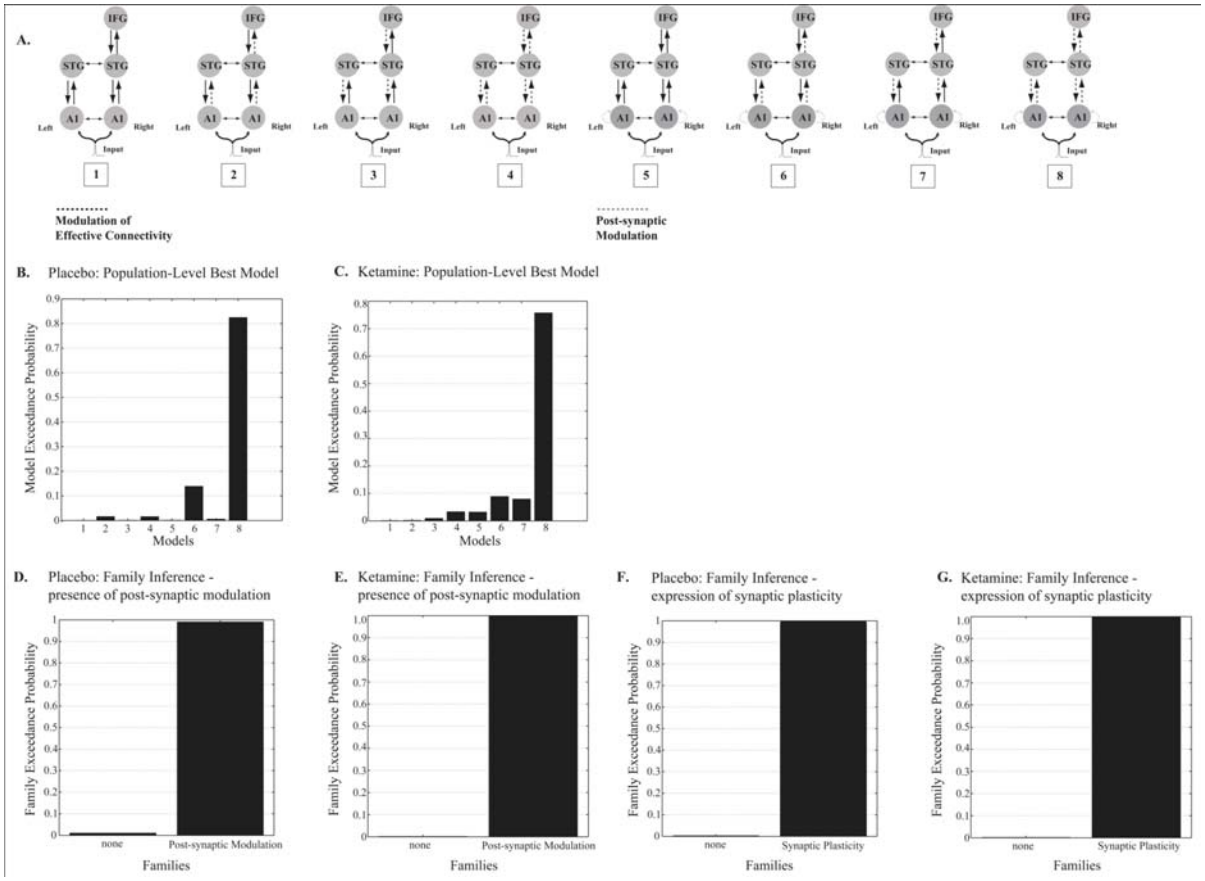

Figure 7: Model specification. (A) The 8 DCMs used for Bayesian model comparison. Auditory input first affects primary auditory cortex, from where activity is propagated to the remaining sources. Dotted lines indicate which model allow for adaptation and synaptic plasticity that are expressed as modulation in post-synaptic gain and effective connectivity for deviant vs. standard tones, respectively. (B and C) Random effects Bayesian model selection showed that the model with synaptic plasticity (modulation of connection strength) in both forward and backward connections as well as adaptation in A1 (post-synaptic gain modulation) had the greatest evidence for both placebo and ketamine conditions. (D and E) Family-wise Bayesian model selection showed that the presence of adaptation (post-synaptic gain modulation) improved models considerably, regardless of the presence of synaptic plasticity. (F and G) Family-wise Bayesian model selection showed that the presence of synaptic plasticity improved models considerably, regardless of the presence of adaptation.

Furthermore, we exploited the factorial nature of our model space to examine the importance of each mechanistic factor (adaptation and synaptic plasticity, respectively) on its own. Random effects family-level BMS showed that “adaptation models” that allowed for post-synaptic gain modulation in A1 (models 5-8) were generally superior to models without adaptation (models 1-4) in both placebo and ketamine conditions (exceedance probabilities >99%), regardless of synaptic plasticity elsewhere in the model (Figs. 7d and 7e). Conversely, models which allowed for the expression of synaptic plasticity at inter-regional connections (models 2-4, 6-8) were generally superior to models without

such plasticity (models 1 and 5) in both placebo and ketamine conditions (exceedance probabilities >99%), regardless of whether the model included adaptation or not (Figs. 7f and 7g).

Effects of ketamine

To examine the effects of ketamine on mechanisms underlying the NMDAR-dependence of the MMN response, we compared the parameter estimates from subject-specific DCMs that were averaged (using BMA) separately for placebo and ketamine conditions. First, we used a multivariate Hotelling's T^2 test to examine whether the distinct sets of parameter estimates encoding neuronal adaptation and short-term synaptic plasticity, respectively, were significantly different between ketamine and placebo conditions. This drug-induced difference was significant for the parameter set representing synaptic plasticity ($T = 14.771$ with $p<0.023$), but not for the parameter set representing neuronal adaptation ($T = 0.217$ with $p = 0.897$). In other words, while adaptation was critical for explaining the MMN (see above), it did not change under ketamine compared to placebo. Based on this result we used, in a second step, univariate post-hoc t-tests, asking where in the network synaptic plasticity was affected by ketamine (i.e., at which of the six forward and backward connections in the model). We found a significant reduction of synaptic plasticity, following ketamine administration, of the forward connection from left A1 to left STG (see Fig. 8 and Table 1). In other words, under placebo, the left A1→STG connection almost doubled in strength when a deviant tone was presented; in contrast, under ketamine, this increase was almost absent (Figure 8; note that the modulatory parameters in DCM for ERPs are scaling coefficients, not additive contributions as in DCM for fMRI).

Table 1 Paired T test results: Reductions in forward and backward modulation in the ketamine compared to the placebo condition.

	Postsynaptic Modulation		Foward Connections			Backward Connections		
	left A1 > left A1	right A1 > right A1	left A1 > left STG	right A1 > right STG	right STG > right IFG	left STG > left A1	right STG > right A1	right IFG > right STG
Z	0.672	0.310	3.148	1.728	1.065	0.114	1.136	0.284
Sig. (2-tailed)	0.501	0.756	**0.001***	0.084	0.287	0.910	0.256	0.776

*FWE $p < 0.05$

Notably, this effect of ketamine on synaptic plasticity remained significant after Bonferroni-correction for multiple comparisons ($t=4.60$, $p<0.001$). Furthermore, there was a trend towards a significant reduction in the forward connection from the right A1 to the right STG ($t=1.55$, $p = 0.14$).

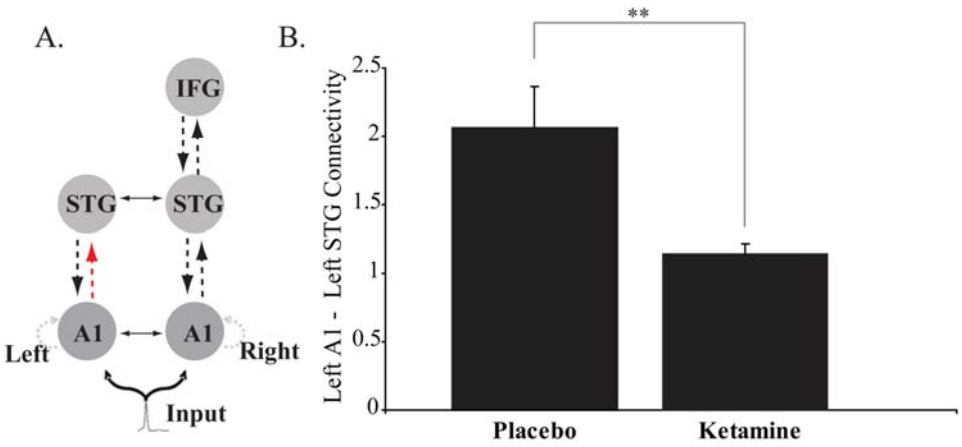

Figure 8 The plasticity of the forward connection from the left A1 to the left STG was significantly reduced after ketamine administration ($p < 0.001$). The y-axis denotes the average value (± SD) of the scaling parameter that indicates changes in connection strength for deviant vs. standard tones.

Finally, we related this selective effect of ketamine on plasticity of the left A1→STG connection to the impact of ketamine on subjects' ASC-R questionnaire scores. Specifically, Schmidt et al. (2011) had reported an effect of ketamine on the "control and cognition" subscale of the ASC, and we now tested, using a simple linear regression analysis, whether this effect of ketamine might be explained through its effects on plasticity of the left A1→STG connection. Indeed, there was a significant linear relation between drug effects on "control and cognition" ratings (score under ketamine minus score under placebo) and drug effects on plasticity (ratios of condition-specific changes in coupling, i.e. Relative plasticity under ketamine vs. placebo) of the left A1→STG connection ($F= 4.45$, $p < 0.006$).

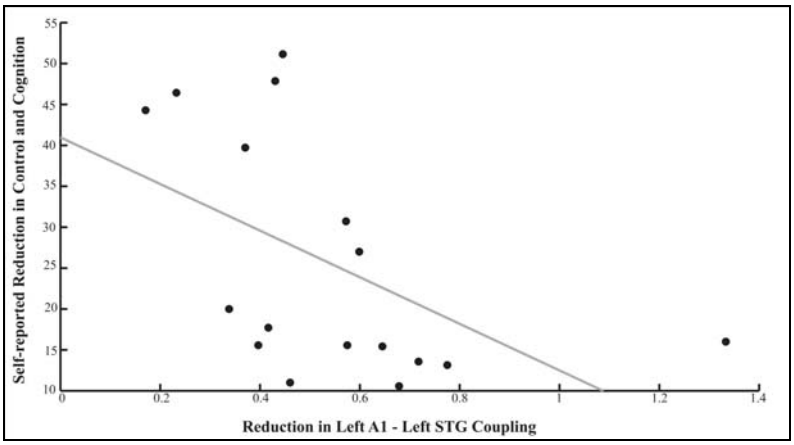

Figure 9 Figure 9: Linear regression indicated a significant relation between drug effects on "control and cognition" ratings (score under ketamine minus score under placebo) and drug effects on plasticity (ratios of modulatory scaling factors, i.e. % plasticity under ketamine vs. placebo) of the left A1→STG connection ($F= 4.45$, $p < 0.006$).

Discussion

In this paper we present a model-based investigation of the physiological mechanisms that underlie the well-established reduction of the MMN following administration of the NMDAR antagonist ketamine. Specifically, we used DCM and BMS to analyze data from a recent study by Schmidt et al. (2011) of healthy volunteers during a roving MMN paradigm with a cross-over double-blind placebo-controlled design. In the following, we summarize the results of our model-based investigations, discuss their implications and consider potential limitations of our study.

In a first step, we verified that we could replicate the results of a previous DCM study of the roving MMN paradigm (Garrido et al., 2008). Specifically, we specified a set of 8 models that differed systematically in (i) whether or not they allowed for a differential expression of adaptation (post-synaptic sensitivity) during standard and deviant stimuli and (ii) which connections were allowed to change – show short-term plasticity – between deviant and standard stimuli. (These models were very similar to those of Garrido et al. (2008) except that we added interhemispheric connections at the level of both primary and secondary auditory areas (Figure 7). These connections do not change the relative evidence for different models, but increase overall model evidence.) Reassuringly, our model selection results replicate those by Garrido et al. (2008): regardless of drug condition, both adaptation in primary auditory cortex and short-term plasticity of forward and backward connections across the auditory hierarchy markedly improved the model evidence (Figure 7). In other words, as postulated by MMN theories resting on the free-energy principle (Garrido et al., 2009b), both adaptation and synaptic plasticity are required to explain the MMN generation *per se*.

While both adaptation and plasticity of forward and backward connections were required to explain MMN, which of these mechanisms, if any, would be attenuated by ketamine? Using Bayesian model averaging (Penny et al., 2010), we asked whether ketamine effects on the MMN generation were reliably models by DCM such that the pharmacological effects were clearly reflected in the models parameters (changes in coupling). To this end we used a multivariate Hotelling's T^2 test, testing separately whether the parameter estimates encoding neuronal adaptation and short-term synaptic plasticity, were significantly different between ketamine and placebo conditions. This drug-induced difference was significant for the parameters representing synaptic plasticity, but not adaptation. We then proceeded to ask, using univariate t-tests, which of the six forward and backward connections were most critical for explaining the ketamine effects. Correcting for multiple comparisons, we found that only plasticity in the forward connection from left A1 to left STG showed a significant change under ketamine, compared to placebo. A similar trend was observed for the homologous forward connection from right A1 to right STG, but this did not quite reach significance.
Finally, we examined whether our model-based estimates of ketamine-induced attenuation of short-term plasticity in the left A1→STG connection correlated with a measure of ketamine-induced change in cognition. The previous study by Schmidt et al. (2011) had found a correlation between relative ketamine-induced impairments of subjective ratings of impaired control and cognition (subsuming items for disordered thought and loss of control over body and thought) and the MMN "slope" under

placebo, which indexes the systematic increase in MMN amplitude with the number of preceding standards (a specific index of prediction error processing). In brief, the previous study showed that MMN expression under placebo predicted the effects of ketamine on introspective ratings of symptoms that are reminiscent of schizophrenic symptoms (e.g., thought disorder). Our present analyses suggest a more fine-grained interpretation of this relationship: our model-based analyses report a significant correlation between ketamine effects on short-term plasticity of the left A1→STG connection and ketamine-induced changes in "control and cognition" ratings. In other words, we empirically demonstrated that blocking NMDARs by ketamine leads to impaired plasticity by reducing changes in connection strength from the left A1 to the left STG, the extent of which predicted significant S-ketamine-induced psychopathology. It is interesting to note that ketamine selectively exerted effects on the left, but not right A1→STG connection. This hemispheric asymmetry is reminiscent of the left-hemispheric dominance of inner speech that has been linked to disordered thought in schizophrenia; e.g., (Strik et al., 2008). However, this is clearly a speculative observation at the present time.

Our results are consistent with the free-energy account of the MMN in that they highlight the importance of both adaptation (in primary auditory cortex) and short-term plasticity (of inter-regional connections) for the generation of the MMN. Put simply, the sensory learning that is assumed to underlie the MMN calls on associative plasticity in the extrinsic connections communicating predictions and prediction errors between levels of the auditory hierarchy. As the oddball is repeated, sensory learning produces more efficient predictions of auditory stimuli and a decrease in effective connectivity of extrinsic connections (as the oddball becomes a standard). Our analyses suggest that this decrease is eliminated by ketamine – consistent with its antagonism of NMDAR–dependent plasticity. Adaptation – or changes in postsynaptic gain – is thought, in the context of predictive coding, to encode the precision of bottom-up information. This precision is itself optimized as a function of stimulus repetition. The present results suggest that this neuromodulatory optimization may be less sensitive to NMDAR blockade.

One point of contention, however, may be that our present analyses identified a predominant impact of NMDAR antagonism on the plasticity of the *forward* connections of the auditory hierarchy. From the perspective of predictive coding, the free energy formulation suggests forward connections convey prediction errors, i.e. phasic signals requiring fast synaptic transmission. In contrast, predictive coding regards backward connections as conveying predictions, which may be of a more modulatory nature and elicit more enduring effects. This view draws on the concept of "driving" forward and "modulatory" backward connections in sensory processing streams (Sherman and Guillery, 1998) and led to proposals (Friston, 2005; Corlett et al., 2011) that forward connections predominantly employ fast AMPARs, whereas the more modulatory backward connections also engage NMDARs, whose time constants are an order of magnitude larger than those of AMPARs. From this perspective, one may thus have expected our DCMs to identify a predominant effect of ketamine on the plasticity of backward, rather than forward, connections. It may be useful to consider, however, that NMDARs, despite their slower time constants compared to AMPARs, are nevertheless ionotropic receptors and are capable of conveying driving effects in the presence of other excitatory inputs (i.e., once the cell membrane is depolarized) (Daw et al., 1993). Indeed, such "driving" effects of NMDARs are

established, e.g., in visual cortex (Fox et al., 1990) and auditory cortex (Kelly and Zhang, 2002). In line with this, the original notion of “driving” and “modulatory” connections, as proposed by Sherman and Guillery (1998), jointly considers AMPARs and NMDARs as ionotropic receptors for driving connections and focuses on metabotropic glutamate receptors (mGluRs) for modulatory (backward) connections. In other words, while it is perfectly plausible that NMDARs play an important role in synaptic transmission along backward connections, “it is unlikely that NMDA receptors only signal predictions and AMPA receptors signal prediction errors; rather there may be a division of labour where AMPA receptors are relatively more engaged in bottom-up and NMDA receptors are relatively more involved in top-down processes” (Corlett et al., 2011). Our present results are in line with this view and imply a less strict dichotomy between AMPAR and NMDAR mediated effects at forward and backward connections, respectively, as considered in previous MMN models.

Having said this, it is important to keep in mind that we used a fairly simplistic model for inferring the physiological mechanisms of the MNN. While the DCM used in this study does distinguish between different neuronal populations (pyramidal cells, granular cells and inhibitory interneurons), it does not distinguish between pyramidal cells in supra- and infragranular layers, which take on different roles within predictive coding schemes (Friston, 2010). Furthermore, while the model does make a distinction between glutamatergic and GABAergic synapses, there is no explicit distinction between fast (AMPA) and slower (NMDA) ionotropic receptors, not to mention the modulatory contributions from mGluRs. The parameter estimates we obtain from our present model are therefore rather coarse, lumped summaries of numerous physiological processes, and the estimates obtained for short-term synaptic plasticity cannot be split up into distinct contributions from different glutamatergic receptors.
There is, however, recent progress in developing DCMs that move towards a much more fine grained representation of synaptic physiology. These “conductance-based” DCMs use a simplified Morris-Lecar formulation to infer the relative contributions of separate ion channel types (with different ligand-/voltage-gated behavior and time constants) to measured potentials (Marreiros et al., 2010). Recently, this model was extended to include an explicit NMDAR representation, rendering it potentially capable of inferring on differential contributions of NMDAR and non-NMDAR mediated transmission at glutamatergic synapses (Moran et al., 2011a). This extended model is currently being validated and when these studies are complete we will re-examine our present data using models of this sort.
Another opportunity to complement the analysis from the present study is to employ recently developed computational models which use the same Bayesian inference framework as DCM but are agnostic about physiological mechanisms. Instead, they enable the investigation of trial-by-trial changes in MMN amplitude from a purely computational (information theoretic) perspective. In other words, they help clarifying which computational quantities (e.g., prediction errors or surprise) are reflected by the trial-by-trial dynamics of MMN expression (Lieder et al., in preparation). These models, once they are fully established, should enable us to examine the effects of ketamine on MMN generation from a complementary perspective.
In summary, the present study has presented a novel model-based characterization of the effects of NMDAR antagonism during the MMN roving paradigm. This study is part of ongoing efforts to establish model-based assays of brain disease processes; a theme that plays a major role in

computational approaches to dissecting the pathophysiology of spectrum diseases, such as schizophrenia, into physiologically well-defined subgroups (Stephan et al., 2009a). A recent proof-of-concept study demonstrated that one can infer, from scalp MEG recordings, dopaminergic effects of NMDA and AMPA receptors (Moran et al., 2011b). Furthermore, several validation studies have demonstrated that estimates of glutamatergic synaptic physiology – obtained using a DCM that is similar to the DCM used in this study – can be obtained from intracerebral and extradural local field potential recordings (Moran et al., 2008; Moran et al., 2011c). The present study has extended this program towards inference on NMDAR mediated synaptic effects from EEG data. Clearly, the present study is only a modest step towards non-invasive, model-based inference on glutamatergic synaptic physiology, and more sophisticated models and further validation studies are needed. Eventually, however, we hope that carefully validated model-based approaches will enable diagnostically useful applications of MMN recordings in the future, e.g., for pathophysiologically grounded diagnostic classification of spectrum diseases such as schizophrenia (Stephan et al., 2006).

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4. Visually Evoked Potentials Yield Dissociable Serotonergic and Glutamatergic Effects of Psilocybin and S-ketamine on Emotional Face Processing

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Personal contribution:
AS, MK, and FXV contributed to the study design of this paper. PAC and AS developed the backward masking paradigms. AS and RB contributed to the conduction of the experiments and AS analyzed the data. AS contributed to the writing of the manuscript, with additional contributions by MK, RB, ES, and FXV, who appears as co-authors in this paper.

Abstract

Emotional expressions trigger increased visual responses, even in the absence of conscious awareness. Although the serotonin and glutamate systems are implicated in emotional processing, their differential contribution to visually evoked responses to non-consciously and consciously perceived emotional facial expressions is less well understood. Here, we used backward masking and event-related potentials (ERPs) recording to investigate the effect of the N-methyl-D-aspartate receptor antagonist S-ketamine and the mixed 5-hydroxytryptamine receptor agonist psilocybin on early visual ERP responses to emotional faces over parieto-occipital brain regions. In a double-blind within-subject placebo-controlled design, S-ketamine and psilocybin, were administrated to two groups of healthy subjects, respectively. Objective threshold for conscious awareness following drug administration was determined by signal detection theory. Early visual ERP responses to fearful, happy and neutral faces were quantified by the valence-specific P100 and N170 either during non-conscious or during conscious processing. Both psilocybin and S-ketamine reduced early visual N170 ERP responses to fearful faces, whereas S-ketamine, but not psilocybin, reduced the N170 ERP response to happy faces. Moreover, the effect of psilocybin and S-ketamine on the N170 ERP response to facial expressions depended on the extent of visual awareness. Our results suggest that psilocybin and S-ketamine differentially contribute to the modulation of visual responses to emotional facial expressions. The assessment of early visual responses to emotional expressions may provide a useful framework to detect pharmacologically induced changes in emotional processing and might also lead to a greater understanding of pharmacological mechanisms underlying emotional processing and its dysfunction in affective disorders.

Key words: emotional face processing, NMDAR, 5-HT, conscious awareness, mood and anxiety disorders.

Introduction

Emotional processing including the recognition of other people's feelings from their facial expression is fundamental to social interaction and behavior. The critical importance of face recognition in the human social functioning is shown by the fact that emotional faces increase neuronal activity relative to neutral faces in specific neural pathways. In particular, increased brain responses to emotional faces have been observed within visual face-selective areas of the brain, even when emotional facial expressions are masked to prevent conscious awareness (Anderson et al., 2011; Demenescu et al., 2011; Kleinhans et al., 2011). Thus, modulation of face-selective responses in the visual cortex by emotional expression might correspond to a fundamental regulatory role of basic emotional signals associated with social appraisal and cognition (Schultz et al., 2003; Singer et al., 2004).
It has been shown that emotional processing is modulated by serotonin (5-hydroxytryptamine, 5-HT). For example, acute selective serotonin reuptake inhibitor (SSRI) administration immediately increases the recognition of fearful and happy faces in healthy subjects (Bhagwagar et al., 2004; Browning et al., 2007; Harmer et al., 2003). The neural mechanisms underlying this effect are not fully understood. An imaging study in healthy humans revealed that SSRI acutely increases visual activity in face-selective areas in response to aversive stimuli (Del-Ben et al., 2005). Thus, it has been proposed that the heightened recognition of fearful faces induced by SSRI (Harmer et al., 2003) may be related to an increased processing in visual areas. Furthermore, previous studies found that acute SSRI administration inhibits visually evoked electrophysiological responses to unpleasant expressions, but enhances the responses to pleasant expressions (i.e. steady-state visual evoked potential latency reductions) (Kemp et al., 2003; Kemp et al., 2004; Nathan et al., 2003). Such changes in emotional processing - increased positive and decreased negative bias - are highly relevant to the action of SSRI treatment in mood and anxiety disorders (Harmer, 2008). Emotional processing is also modulated by glutamatergic manipulations. Specifically, a functional imaging study in healthy humans revealed that the visual response to fearful faces is abolished after the administration of the N-methyl-D-aspartate (NMDA) receptor antagonist ketamine (Abel et al., 2003). Taken together, these findings indicate that acute serotonergic and glutamatergic manipulations change emotional processing as indexed by the assessment of visual cortex responses to facial expressions.

Recent studies used event-related potential (ERP) recording to study the time course of neural responses to non-conscious versus conscious processing of facial expressions within a masking paradigm (Liddell et al., 2004; Pegna et al., 2008; Williams et al., 2004). Backward masking is a key experimental paradigm to investigate neural responses to below-awareness stimuli (Tamietto and de Gelder, 2010). The two ERP components P100 and N170 are related to early visual processing and are suitable to distinguish between emotional and neutral faces. The P100 is an early positive occipital potential, peaking at around 80-120 ms post-stimulus and reflects rapid extraction of information related to emotion or salience that occurs before more fine-grained perceptual analyses are completed (Vuilleumier and Pourtois, 2007). Modulation of the P100 has been shown with fearful (Fichtenholtz et al., 2009; Pourtois and Vuilleumier, 2006), angry (Santesso et al., 2008), and positive expressions (Batty and Taylor, 2003; Brosch et al., 2008). The N170 is a negative occipito-temporal potential at

approximately 170 ms post-stimulus and is associated with structural encoding of facial configurations (Itier and Taylor, 2004; Rossion and Jacques, 2008). The N170 is also increased by emotional relative to neutral faces (Blau et al., 2007; Leppänen et al., 2007), even when faces are subliminally presented below visual awareness (Pegna et al., 2008; Smith, 2011). In the current study, we use backward masking to investigate how early visually evoked ERP responses to emotional facial expressions during non-conscious and conscious processing are modulated by the NMDA receptor antagonist S-ketamine and the mixed 5-HT receptor agonist psilocybin. Both S-ketamine and psilocybin modulate neuronal activity in circuits implicated in the regulation of mood and anxiety (Vollenweider and Kometer, 2010) and were suggested to have a clinical potential. Acute ketamine administration ameliorates depressive symptoms in treatment-resistant depression within a few hours persisting for several days (Diazgranados et al., 2010; Zarate et al., 2006), while acute psilocybin administration in healthy subjects leads to heightened mood, increased emotional excitation and sensitivity (Studerus et al., 2010b) and decreases anxiety in terminal cancer patients within a month (Grob et al., 2011). To investigate further the neuronal underpinnings of the effect of psilocybin and S-ketamine on emotional processing, first we examined whether psilocybin and S-ketamine affect visually evoked ERP responses to facial expressions in a valence specific manner, and second whether these effects vary as a function of visual awareness. Specifically, signal detection theory was applied to behaviorally establish objective threshold for conscious awareness irrespective of subject's response bias. Furthermore, early visually evoked ERP responses to fearful, happy and neutral faces were quantified by the P100 and N170 during non-conscious compared to conscious processing.

Method

Participants

Healthy subjects were recruited through advertisement from the local universities and were then separated into two groups (S-ketamine group: N = 21, [male: 12], mean age = 26 ± 5.39 y; psilocybin group: N = 21, [male: 13], mean age = 23 ± 2.22 y, all were students). Subjects were healthy according to medical history, clinical examination, electrocardiography, and blood analysis. Subjects were screened by the DIA-X diagnostic expert system (Wittchen and Pfister, 1997a), a semi-structured psychiatric interview to exclude those with personal of family (first-degrees relatives) histories of major psychiatric disorders, and by standard psychometric instruments including the Symptom Checklist (SCL-90–R) (Derogatis, 1994a) and the State Trait Anxiety Inventory STAI (Spielberger et al., 1970). Furthermore, subjects replied to the Mini-International Neuropsychiatric Interview (M.I.N.I.), a brief, structured psychiatric interview (Sheehan et al., 1998). No subjects had to be excluded using these criteria. We verified the absence of a history of drug dependence by urine drug-screening and a self-made consumption questionnaire. In the S-ketamine group, seven subjects were occasional smokers (<10 cigarettes/day), eight subjects reported a sporadic or rare cannabis use in the past (<3 joints/month), and two subjects reported experiences with MDMA (three pills lifetime). In the psilocybin group, eight subjects were occasional smokers (<6 cigarettes/day), eight subjects reported a sporadic or rare cannabis use in the past (<2 joints/month), one subject reported experiences with MDMA (two pills lifetime), and two reported experiences with psilocybin (two administrations lifetime). All subjects were free of any medication for at least 3 weeks before the experiment. This study was approved by the Ethics Committee of the University Hospital of Psychiatry, Zurich. After receiving a written and oral description of the aim of this study, all participants gave written informed consent statements before inclusion. The use of psilocybin was authorized by the Swiss Federal Office for Public Health, Department of Pharmacology and Narcotics, Berne, Switzerland.

Drug administration

In both groups, subjects underwent two sessions (placebo/active drug) in a balanced and random order at an interval of at least 2 weeks. Both subject and principal investigator were blind to drug order. Subjects stayed monitored until all drug effects had worn off, and were then released into the custody of a partner. For the S-ketamine/placebo infusion, an in-dwelling catheter was placed in the antecubital vein of the nondominant arm. Once the subject was ready, a bolus injection of 10 mg over 5 min was given. Following 1 min break, a continuous infusion with 0.006mg/kg per min was administered over 80 minutes. To keep S-ketamine's plasma level fairly constant, the dose was reduced every ten minutes by 10% (Feng et al., 1995; Vollenweider et al., 1997b). In the placebo session, the same procedure was followed and an infusion of physiological sodium chloride solution and 5% glucose was given. Psilocybin (115 µg/kg) and lactose placebo were orally administered in gelatin capsules of identical number and appearance. The doses of S-ketamine and psilocybin selected in this study were previous shown to produce similar overall effects on subjective experiences

including robust emotional effects and only moderate visual disturbances (Gouzoulis-Mayfrank et al., 2005; Hasler et al., 2004; Studerus et al., 2010b; Vollenweider and Kometer, 2010).

Psychological assessment

The Altered State of Consciousness (ASC) questionnaire, a visual analogue and self-rating scale, was used to assess the subjective psychological effects induced by S-ketamine and psilocybin (Dittrich, 1975; Dittrich, 1998). A recent evaluation study of the ASC questionnaires has constructed eleven new lower order scales (Studerus et al., 2010a), which were analyzed in this study. The ASC questionnaire was given 240 min post-treatment to rate retrospectively their experiences since drug intake.

Stimuli and backward masking procedure

As stimulus material we took black and white photographs taken from the Ekman–Friesen series (Ekman and Friesen, 1976). To limit the contribution of low-level effects of the photographs, faces were modified using Adobe Photoshop, so that only the eyes, eyebrows, nose and mouth were visible features, while other characteristics such as the skin texture, wrinkles, etc. were hidden. This modification was intended to prevent subjects from utilizing a strategy to discriminate emotional from neutral facial expressions by using such low-level cues. The final facial images subtended a visual angle of 3° horizontally and 4.4° vertically and were displayed in the center of a CRT monitor. Backward masking procedures were generated by E-prime software (Schneider et al., 2002) (Fig. 1). Timing issues were confirmed by using an oscilloscope. Subjects first underwent a mismatch negativity event-related paradigm for 15 minutes, which has been published elsewhere (Schmidt et al., 2011). Emotional measures were started 25 min after S-ketamine infusion and 110 min following psilocybin administration during the known plateau (Hasler et al., 2002; Passie et al., 2002).
Facial affect discrimination: Two discrimination tasks were designed to establish thresholds for conscious awareness, i.e. to determine the time point, at which subjects can distinguish emotional from neutral expression above chance level. In a first task, subjects had to discriminate fearful from neutral faces, while in a second task they had to discriminate happy from neutral faces. For each discrimination task, target faces consisted of neutral, fearful and happy faces, respectively, and were presented for 20, 30, 50, 90 or 170 ms (Williams et al., 2004). Target faces were immediately followed by a neutral mask lasting for 150 ms. Participants performed 5 blocks of 40 trials (target-mask pairs) for each of both tasks, in which target faces were randomly presented with equal probability. Before each target-mask pair, a fixation cross was presented for 1000 ms. Subjects made an objective forced-choice decision about the valence of the target face (fearful/happy vs. neutral) via button-press after each target-mask pair.

EEG/ERP recording: During ERP recording, stimuli were identical to those used during facial affect discrimination. Target faces including neutral, fearful or happy faces and were immediately followed by a neutral mask for 150 ms. Each trial began with a fixation cross that lasted for 2000 ms. The presentation time of the target face depended on the condition, 10 ms during non-conscious and 200

ms during conscious awareness (Williams et al., 2004). No subject response (botton-press) was required. Participants were given instructions that pairs of target-mask faces would be presented and that they would be asked questions about the first faces after testing.

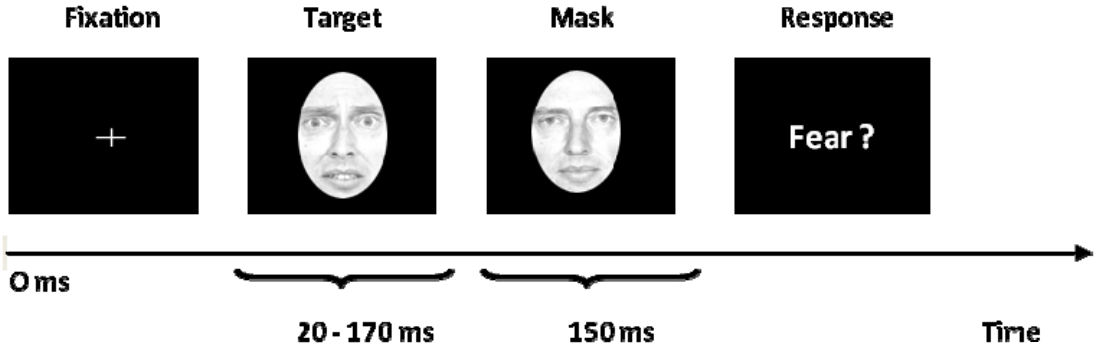

Figure 1 Schematic of the backward masking paradigm. During the discrimination threshold tasks, a fixation cross was first presented for 1000 ms, followed by the target face, which lasted for 20, 30, 50, 90 or 170 ms, respectively. Finally, a neutral mask was presented for 150 ms. After each target-mask pair subjects were asked to answer via key press. During ERP recording, the fixation cross was presented for 2000 ms. The presentation time for the target faces was 10 ms for non-conscious processing, and 200 ms for conscious processing.

EEG/ERP recording

EEG recordings were made from 64 scalp electrodes using the ActiveTwo system (Biosemi, The Netherlands). The horizontal electroocculogram (EOG) was recorded from electrodes attached on the outer canthus of each eye. Similarly, vertical EOG was recorded from electrodes attached infraorbitally and supraorbitally to the left eye. All electrodes were active silver/silver chloride electrodes and the offset of all electrodes was below 25mV. Data were recorded at a sampling rate of 512 Hz. The common mode sense (CMS) active electrode and the driven right leg (DRL) passive electrode were used as reference and ground electrodes, respectively (see http://www.biosemi.com/faq/cms&drl.htm for more details on this setup).

For ERP analysis, independent component analysis was used to remove artifacts due to eye movements and blinks (Lee et al., 1999). The EEG data were recalculated offline against average reference. Then, epochs with a 200-ms prestimulus baseline and a 500-ms post-stimulus interval were constructed. Epochs with amplitudes that exceeded ± 100 μV at any electrode were excluded from further averaging. After artifact rejection, epochs were averaged for each subject and were digitally filtered with a band-pass filter (1-30 Hz). P100 and N170 ERPs were scored at electrodes P08/P8/P10/O2 (right hemisphere) and PO7/P7/P9/O1 (left hemisphere) as peak positivity/negativity relative to baseline within the 130-200 ms and 150-250 ms window latency, respectively, as previously described (Frühholz et al., 2011; Jaworska et al., 2010; Wronka and Walentowska, 2011).

Statistical analysis

Discrimination performances were analyzed according to signal detection theory (STD), which provides a measure of sensitivity that is independent of subject's response bias (Macmillan and Creelman, 1991). Threshold settings were determined by Students t-tests against chance level (d' = 0). Sensitivity indices (d') were further subjected to a repeated measurement analysis of variance (ANOVA) with the within-subject factors *target duration* (20, 30, 50, 90, 170 ms), *valence* (fearful, happy) and *treatment* (placebo, drug), as well as with the between-subject factor *group* (S-ketamine, psilocybin). Based on significant main effects or interactions, Fisher's least significant difference tests (LSD) were performed. Repeated measurement ANOVA on the ASC data with *treatment* and *scale* as within-subject factors and *group* as between-subject factor was used to examine drug-induced psychological effects. P100 and N170 ERP data for each group were subjected to repeated measurement ANOVAs with the within-subject factors *treatment* (placebo, drug), *target duration* (non-conscious, conscious), *valence* (fearful, happy and neutral) and *laterality* (right, left). To compare both drug effects on the specific ERPs, we further computed the relative change scores between placebo and drug conditions (placebo/drug). Change scores were subjected to a repeated-measures ANOVA with the within-subject factors *target duration* (non-conscious, conscious), *valence* (fearful, happy and neutral) and *laterality* (right, left); and with the between-subject factor *group*. Where the ANOVA null hypothesis of equal means was rejected, we used LSD *post-hoc* tests.

Results

Facial affect discrimination

Students t-tests against d' = 0 revealed that for the discrimination of fearful relative to neutral faces (Fig. 2), d' values at 20 ms for both groups under placebo did not differ significantly from chance level (mean d' = 0.07, SD = 0.32) (p's = 0.15), while d' values at 30 ms were clearly above chance level (mean d' = 0.33, SD = 0.48) (p's < 0.00001). Following drug administration, d' values at 30 ms were still not above chance level (mean d' = 0.08, SD = 0.68, p's = 0.46), whereas performances at 50 ms reached significance (mean d' = 0.28, SD = 0.36, p's < 0.0001). Thus, the point at which subjects can discriminate fearful from neutral facial expressions with above-chance accuracy was shifted relative to placebo after both S-ketamine and psilocybin administration. During happiness discrimination (Fig. 3), all d' values significantly varied from chance level, irrespective of treatment.

Repeated-measures ANOVA revealed that d' values significantly increased across *target duration* [$F(4,160) = 195.19$; $p < 0.00001$; $\eta^2 = 0.83$]. In general, d' values for happy faces were more pronounced than for fearful faces ($p < 0.05$), as indicated by a significant main effect for *valence* [$F(1,40) = 4.15$; $p < 0.05$; $\eta^2 = 0.09$]. Furthermore, a significant main effect for *treatment* was found [$F(1,40) = 36.04$; $p < 0.00001$; $\eta^2 = 0.47$]. Particularly, a *treatment* × *valence* × *group* interaction [$F(1,40) = 4.11$; $p < 0.05$; $\eta^2 = 0.09$] revealed that this treatment effect depended on the valence and on the specific drug used. Although S-ketamine significantly reduced d' values for both fearful (p <

0.001) and happy faces ($p < 0.001$) relative to placebo, psilocybin did not affect d' values for happy faces ($p = 0.87$).

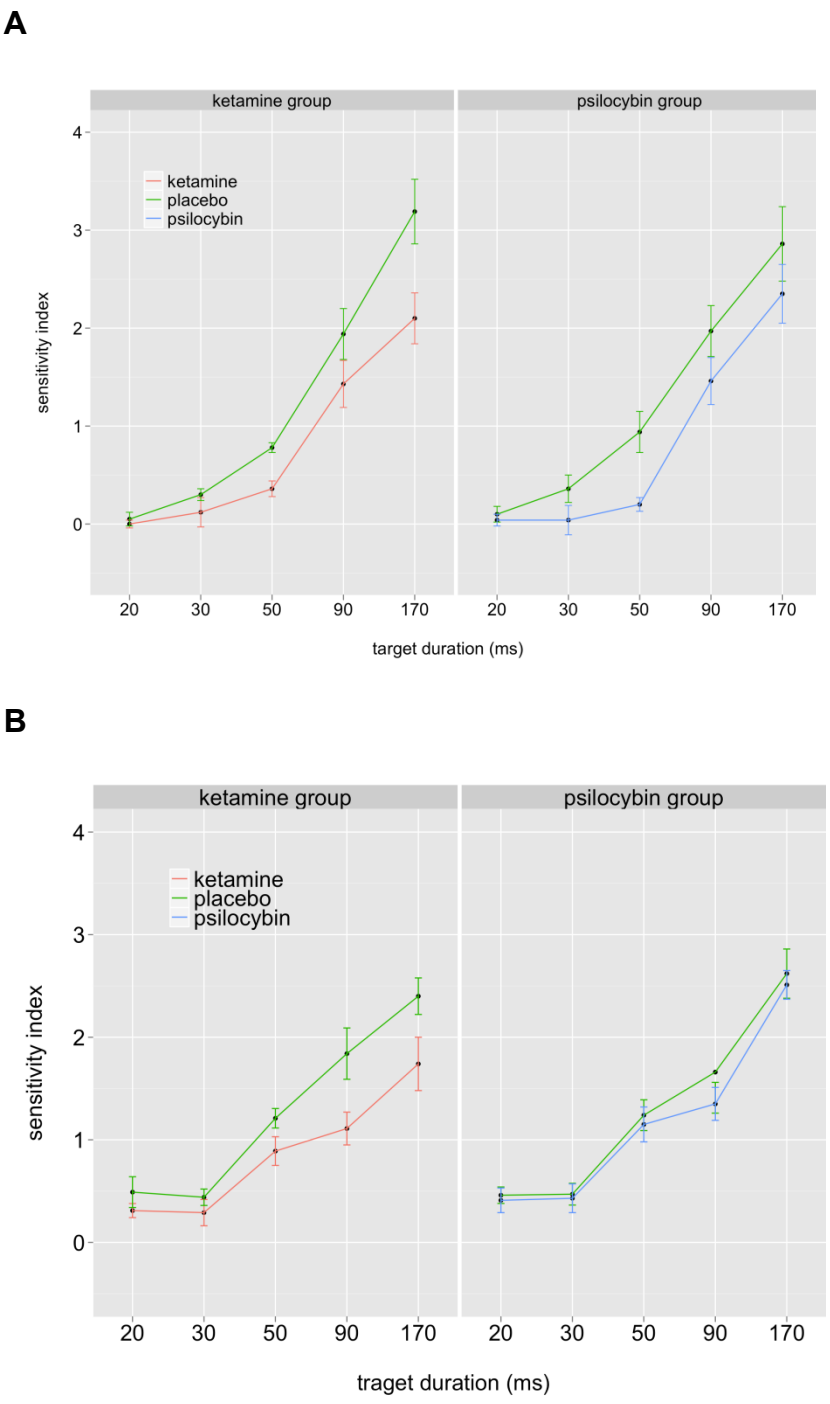

Figure 2 Sensitivity indices (d') ± SE represented as a function of target duration during **A)** fear discrimination and **B)** happiness discrimination. Notably, S-ketamine significantly reduced d' values for fearful and happy faces, while psilocybin only reduced d' values for fearful but not for happy faces.

ERP results

Mean of grand averages over both hemisphere of the P100 and N170 ERP during non-conscious and conscious processing are shown in Figure 3.

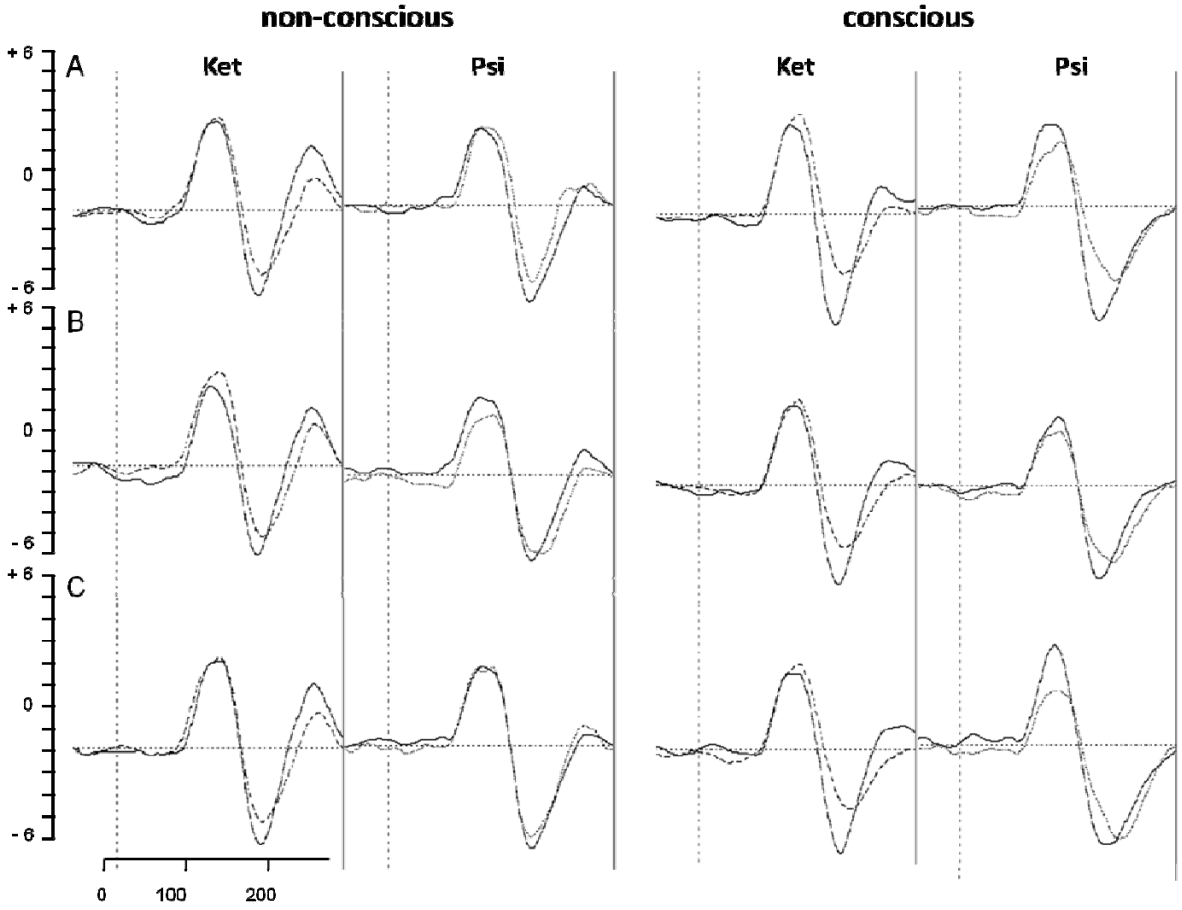

Figure 3 Mean of grand averages over both hemispheres of the P100 and N170 ERP for fearful (A), neutral (B) and happy faces (C) during non-conscious (left) and conscious awareness (right) following placebo (solid line), S-ketamine (Ket: dashed line) and psilocybin (psi: dotted line) administration, respectively.

P100 ERP

Repeated-measures ANOVA revealed that P100 amplitudes were generally more pronounced over right compared to left electrodes both in the S-ketamine [$F(1,20) = 18.23$; $p < 0.001$; $\eta^2 = 0.48$] and in the psilocybin group [$F(1,20) = 22.22$; $p < 0.001$; $\eta^2 = 0.53$]. No other main effects or interactions were observed for P100 amplitudes in both groups. Comparing the effect of S-ketamine and psilocybin, repeated-measures ANOVA on the change scores for the P100 ERP showed no main effects and interactions, reflecting that the effect of S-ketamine and psilocybin on the P100 ERP were broadly similar.

N170 ERP

Repeated-measures ANOVA on the S-ketamine data revealed that N170 amplitudes were generally more pronounced over right compared to left electrodes, indicated by significant main effects for *laterality* ($F(1,20) = 25.97$; $p < 0.0001$; $\eta^2 = 0.56$). Furthermore, a main effect of *treatment* was found ($F(1,20) = 8.73$; $p < 0.01$; $\eta^2 = 0.30$), reflecting an overall attenuation of the N170 amplitude following S-ketamine administration (Fig. 4 *left*). The *treatment* × *laterality* interaction ($F(1,20) = 46.70$; $p < 0.00001$; $\eta^2 = 0.7$) showed that this treatment effect occurred only over right electrodes ($p < .000001$) but not over left electrodes ($p = .14$). Furthermore, the treatment effect also depended on the target duration, revealed by the *treatment* × *target duration* interaction ($F(1,20) = 4.75$; $p < 0.05$; $\eta^2 = 0.19$). LSD p*ost-hoc* testing showed that S-ketamine's effect on the N170 amplitude was more pronounced during conscious ($p < 0.00001$) than non-conscious awareness ($p < 0.001$).

Repeated-measures ANOVA on the psilocybin data revealed significant main effects for *laterality* ($F(1,20) = 39.43$; $p < 0.00001$; $\eta^2 = 0.66$) and *treatment* ($F(1,20) = 14.21$; $p < 0.01$; $\eta^2 = 0.42$), reflecting the more pronounced response over right relative to left electrodes ($p < 0.00001$) and the general reduction by psilocybin relative to placebo ($p < 0.01$). This treatment effect was found only over right electrodes ($F(1,20) = 6.61$; $p < 0.05$; $\eta^2 = 0.25$). Furthermore, the *laterality* × *treatment* × *target duration* interaction ($F(1,20) = 4.52$; $p < 0.05$; $\eta^2 = 0.18$) revealed that the N170 reduction over right electrodes was more pronounced during conscious ($p < 0.000001$) compared to non-conscious awareness ($p < 0.01$). However, a *treatment* × *valence* interaction was found ($F(2,40) = 5.92$; $p < 0.01$; $\eta^2 = 0.23$). Post-hoc testing revealed that psilocybin significantly reduced the N170 amplitudes in response to fearful ($p < 0.000001$) and neutral faces ($p < 0.01$), but not to happy faces ($p = 0.1$) (Fig. 4 *right*).

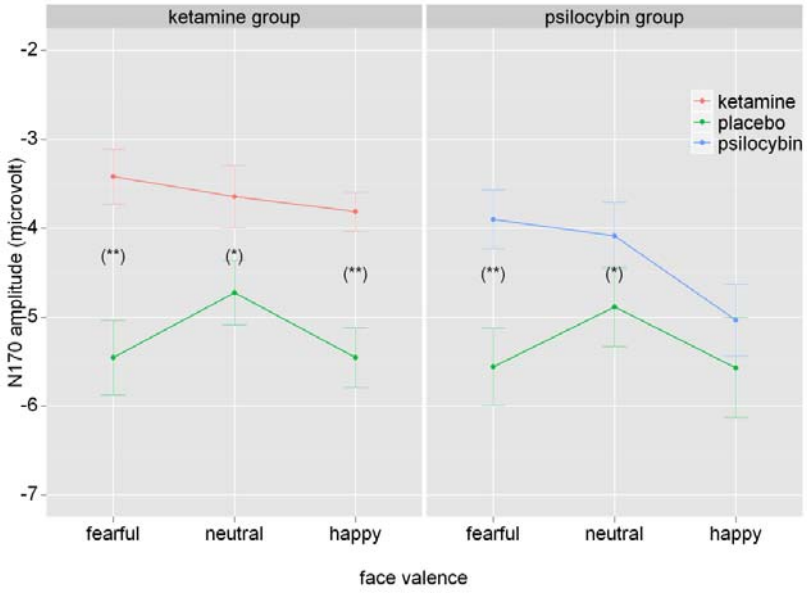

Figure 4 Mean N170 amplitudes ± SE over right electrodes for fearful, neutral and happy faces under S-ketamine (red line), psilocybin (blue) and placebo (green). Note: Significant differences between treatment conditions at $^{(*)}$ $p < 0.01$ and at $^{(**)}$ $p < 0.00001$.

Comparing the effects of psilocybin and S-ketamine on the N170, repeated-measures ANOVA on the change scores revealed a significant valence × *group* interaction ($F(2,80) = 5.19$; $p < 0.01$; $\eta^2 = 0.11$). *Post-hoc* testing showed that S-ketamine and psilocybin reduced the N170 amplitudes in response to fearful ($p = 0.20$) and neutral faces ($p = 0.66$) similarly, whereas happy faces were reduced only by S-ketamine, but not by psilocybin ($p < 0.05$) (Fig. 5).

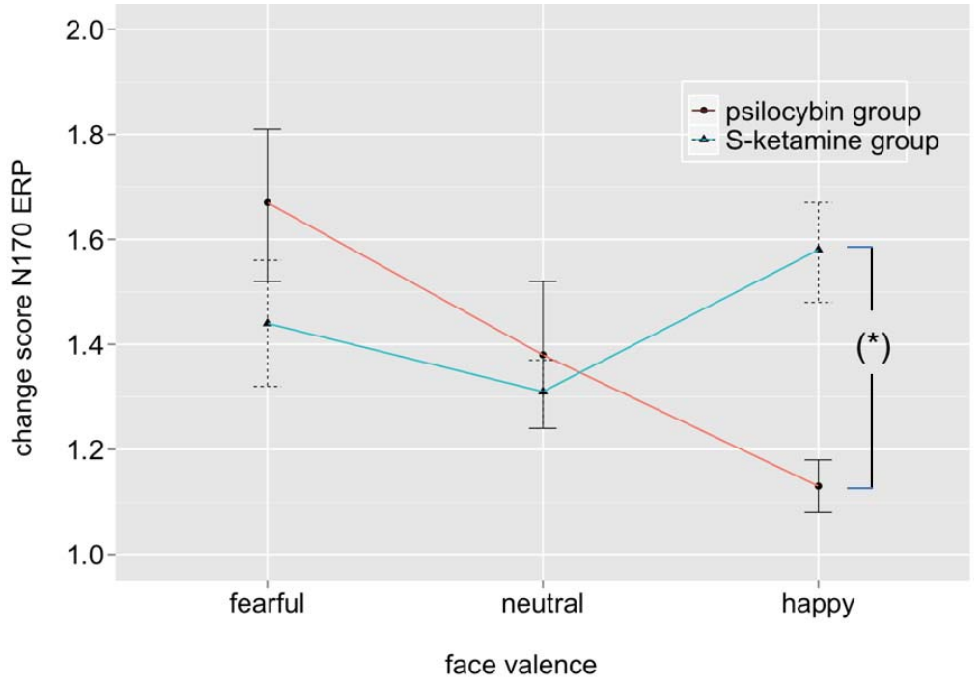

Figure 5 Mean change scores of N170 ERP ± SE depending on the face valence. Notably, the N170 ERP reduction for fearful and neutral faces was comparable among both drugs, but the N170 ERP for happy faces was significantly more reduced after S-ketamine (dotted line) than psilocybin exposure (solid line). $^{(*)}$ indicates a significant difference (LSD) at $p < 0.05$ between the effect of S-ketamine and psilocybin on happy faces and $^{(**)}$ indicates the significant difference at $p < 0.001$ between psilocybin's effect on fearful and happy faces.

Psychological assessment

Both S-ketamine and psilocybin produced similar alterations on the global ASC scores (Fig. 6). ANOVA on the ASC data revealed significant main effects for *treatment* ($F(1,40) = 80.99$; $p < 0.00001$; $\eta^2 = 0.67$) and *scale* ($F(11,440) = 9.73$; $p < 0.000001$; $\eta^2 = 0.20$). A triple *treatment* × *scale* × *group* interaction indicated significant differences between both drug effects on specific scales [$F(11,440) = 5.35$; $p < 0.00001$; $\eta^2 = 0.12$]. *Post-hoc* testing showed that S-ketamine increased all scales relative to placebo (p's < 0.01), expect for anxiety ($p = 0.09$), while psilocybin increased all scales (p's < 0.01), expect for auditory alterations ($p = 0.42$) and anxiety ($p = 0.36$). Moreover, *post-hoc* analysis showed that S-ketamine produced significantly higher scores than psilocybin for disembodiment ($p < 0.000001$), auditory alterations ($p < 0.05$) and for impaired control and cognition ($p < 0.05$). Otherwise, psilocybin produced more severe elementary imagery than S-ketamine ($p < 0.01$).

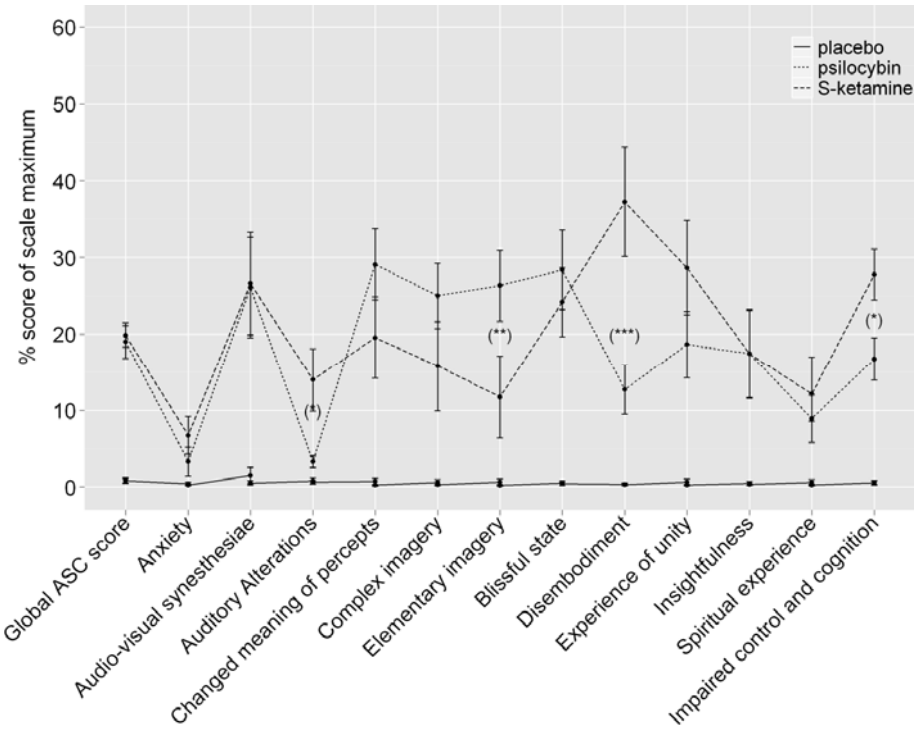

Figure 6. Effects of S-ketamine (dashed line) and psilocybin (dotted line) on the ASC scales. Mean scores and ± SE (both n= 21). Note: $^{(*)}$ indicates significant differences (LSD) between drugs at $^{(*)}$ $p < 0.05$, at $^{(**)}$ $p < 0.01$ and $^{(***)}$ at $p < 0.000001$. Symptoms scores were expressed as percent of scale maximum.

Discussion

We investigated how early visually evoked ERP responses over parieto-occipital brain regions during conscious compared to non-conscious emotional face processing are altered under the NMDAR antagonist S-ketamine and the mixed 5-HT receptor agonist psilocybin. First, both psilocybin and S-ketamine reduced early visual responses to fearful faces as expressed by a reduced N170 response, whereas N170 responses to happy faces were reduced only by S-ketamine. Second, the S-ketamine- and psilocybin-induced reduction of the N170 response depended on the extent of visual awareness.

According to several source modeling and functional magnetic resonance imaging (fMRI) studies (Deffke et al., 2007; Rossion et al., 2003b; Sadeh et al., 2010), the generators of the N170 ERP have been localized to the fusiform gyrus (FG), which encodes the structural configuration of facial features. Because we have performed an analysis in sensor space and because EEG sensor signals result from a mixture of neuronal sources, one should be cautious to relate the present findings to neural sources in specific locations. In other words, the N170 does not necessarily correspond to the FG, and the following discussion should be read with this caveat in mind. Nevertheless, consistent with other reports investigating the acute effect of SSRI on visual responses to emotional expressions (Kemp et al., 2003; Kemp et al., 2004; Nathan et al., 2003), reduced visual responses to fearful faces were found in this study after acute administration of the mixed 5-HT receptor agonist psilocybin. However, contrary to the finding that citalopram enhances visual responses to pleasant expressions (Kemp et al., 2004), we found no alteration of N170 responses to happy faces under psilocybin. This differential effect of psilocybin and citalopram on happy face processing may be due to different electrophysiological measures used in these studies or to the different pharmacological effects of psilocybin and citalopram on the 5-HT system. While SSRI's increase 5-HT brain levels (Elliott et al., 2011; Nutt et al., 1999) psilocybin and its active metabolite psilocin are direct agonists at specific 5-HT receptors (Blair et al., 2000; Nichols, 2004b). That the different pharmacological mechanism of action of psilocybin and SSRI's may be critical is further supported by previous studies using the same ERP marker as used in our study. These studies reported that acute citalopram had no modulatory effects on the N170 in healthy subjects (Kerestes et al., 2009; Labuschagne et al., 2010).
Discussing the effect of S-ketamine's on visually evoked ERP responses to emotional faces, the only work with reference to our result is a previous fMRI study, which explored the neural correlates following ketamine administration during emotional face processing (Abel et al., 2003). The key finding of this study was that the neuronal response in limbic and visual structures during placebo was ameliorated in the amygdala and significantly reduced in the FG following ketamine administration. The authors suggested that this ketamine-induced reduction in neuronal responses to emotional stimuli in limbic and visual regions is associated with the emotional blunting and depersonalization phenomena that are evident in ketamine states (Krystal et al., 1994; Malhotra et al., 1996; Vollenweider et al., 1997b). This interpretation is consistent with the present finding that S-ketamine reduced the N170 not only in response to fearful but also to neutral and happy faces, reflecting an overall emotional blunting of visually induced neural responses.

The importance of the FG in emotional processing is further evidenced by the finding of a functional relationship between object discrimination performance and FG activity. Particularly, FG activity was shown to increase gradually with subjective rating of recognition success (Bar et al., 2001). An identical relationship was also suggested following citalopram administration in healthy subjects (Harmer et al., 2003). Particularly, it has been proposed that the enhanced fear detection in healthy subjects treated with citalopram (Harmer et al., 2003) may be due to the enhancement of visual processing in the FG (Del-Ben et al., 2005). Assuming that the EEG source of the N170 ERP response to facial expressions is localized in the FG (Deffke et al., 2007; Rossion et al., 2003a; Sadeh et al., 2010), our results support and extend such an relationship by showing that the valence-specific modulations during facial affect discrimination by psilocybin and S-ketamine is associated with the drug-induced N170 modulation. Therefore, it is conceivable that the effects on the N170 might reflect drug-specific modulation of FG activity.

In the following section we suggest potential neurobiological mechanisms underlying our key findings. The increased visual response to relevant emotional expressions is likely mediated via rich interconnections between the FG and the amydgala (Amaral et al., 2003; Freese and Amaral, 2005), the coupling of which is additionally strengthened during attentive viewing of affective faces (Fairhall and Ishai, 2007; Herrington et al., 2011). This facilitation may relate to a heightened sensitivity to visual stimuli with emotional relevance (Lane et al., 1999; Lang et al., 1998). Furthermore, emotional face processing also involves prefrontal areas, which are anatomically connected with the FG and the amygdala (Dima et al., 2011). Interestingly, both S-ketamine and psilocybin were found to deactivate the amygdala and to increase prefrontal neural activity (Vollenweider and Kometer, 2010). Thus, it is arguable that the psilocybin- and S-ketamine-induced reduction of the N170 response to fearful faces may be due to a functional alteration in this amygdala-prefrontal network. However, why psilocybin and S-ketamine had dissociable effects on happy face processing is difficult to derive from the present data. A possible explanation could be that S-ketamine and psilocybin differentially modulate circuitries responsible for the processing of positive expressions, because the processing of positive information such as happy faces also involves reward-related areas (Adolphs, 2003; Ishai, 2007; Singer et al., 2004) and further because the N170 showed priming effects as a function of reward (Marini et al., 2011). However, this is highly speculative, and there are a number of other structures involved in face processing and social cognition, which could be differentially modulated after psilocybin and S-ketamine administration. Thus, an important future direction will be to elucidate these valence-specific effects of psilocybin and S-ketamine on the functional integration within the face processing network using imaging techniques and effective connectivity analysis as used in previous studies (David et al., 2006b; Dima et al., 2011; Fairhall and Ishai, 2007; Herrington et al., 2011).

Another key finding of this study was further that the psilocybin- and S-ketamine-induced reduction of the N170 was more pronounced during conscious compared to non-conscious awareness. Numerous studies have described an increase of the N170 with selective attention (Gazzaley et al., 2005; Wronka and Walentowska, 2011), suggesting top-down attentional control. In particular, the visual cortex receives top-down modulation from frontal and parietal areas in relation to visual attention (Bressler et al., 2008) in the time range of the N170 (Rose et al., 2005). In this view, several studies

reported that psilocybin attenuates attentional performances (Carter et al., 2005; Gouzoulis-Mayfrank et al., 2002; Quednow et al., 2011). A recent study examined the influence of psilocybin on the spatiotemporal dynamics of object completion and found a dose-dependent reduction of the N170 response (Kometer et al., 2011). They suggested that this reduction might reflect a psilocybin-induced failure to allocate attention. Similarly, previous evidence revealed that ketamine produce cognitive deficits including impairments of attention (Krystal et al., 1994; Morgan et al., 2004; Newcomer et al., 1999). Therefore, we suggest that the more pronounced reduction of psilocybin and S-ketamine on the N170 during conscious relative to non-conscious processing indicates a drug-induced reduction of attentional resources.

To conclude, our results suggest that the glutamate and serotonin system differentially contribute to the modulation of visual responses to emotional facial expressions in healthy human subjects. Unraveling the role of early visual responses to emotional facial expressions might allow detecting pharmacologically induced changes in emotional processing and might also help to better understand the pharmacological mechanisms underlying the pathophysiology of facial processing biases, which are key impairments in several mood and anxiety disorders. In relation to this, previous studies have shown that a single dose of ketamine in treatment-resistant depression can produce significant antidepressant effects within a few hours persisting for several days (Diazgranados et al., 2010; Zarate et al., 2006). Given that psilocybin selectively reduced negative but not positive emotional processing, it might provide another promising agent to adjust dysfunctional emotional processing biases in mood and anxiety disorders.

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Statement of interest

None.

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5. General Discussion

The studies presented in this thesis outline two distinct perspectives for the experimental use of glutamatergic and serotonergic psychedelics in psychiatric research. On the one hand, we demonstrated how the dissociative NMDAR antagonist S-ketamine and the classical hallucinogen psilocybin, which preferentially activate 5-HT_{2A}R, can be used to investigate the formation of psychotic symptoms. On the other hand, we provided an approach how S-ketamine and psilocybin can serve as research agents to physiologically investigate the role of serotonin and glutamate in emotional processing. In the following, I discuss the present findings chapter-by-chapter by expanding the paper discussion sections. Discussing model psychoses, I relate the results of *chapter 2* to a hypothetical framework centered upon learning and inference, namely to predictive coding models. This theoretical framework assumes that every neural system forms expectations about their sensory input based on previous experiences, and if those expectations do not precisely match with the actual input, the neural system adjusts its expectations by learning and inference to render future inputs more predictable. In *chapter 3*, we provide a computational model-based approach, which is guided by a free-energy perspective on MMN to explain the known NMDAR-mediated disruption of the MMN expression. This means that we provide a possible explanation by using computational modeling how and where in the hierarchical network underlying the MMN generation the NMDAR blockade did disrupt the processing of PEs. In *chapter 4*, we used emotional facial expressions to investigate further the neuronal underpinnings of serotonergic (via psilocybin) and glutamatergic (via S-ketamine) manipulations on emotional processing. Specifically, we assessed how psilocybin and S-ketamine affect visually evoked responses to facial expressions in a valence specific manner, and second whether these effects vary as a function of visual awareness. I discuss these findings by providing possible neurobiological mechanisms. As a last point, I show that the visual responses (N170 ERP) obtained in *chapter 4* speak to the same underlying idea as the auditory responses (MMN ERP) assessed in the model psychosis section *(chapter 2 and 3)*, in particular to predictive coding models or more generally to hierarchical inference in the brain.

5.1. The Role of Glutamate and Serotonin in Models of Psychosis and Schizophrenia

Discussion of Chapter 2

In this study, we used a roving MMN paradigm to compute PEs in healthy humans receiving either the NMDAR antagonist S-ketamine or the preferential 5-HT_{2A}R agonist psilocybin. We physiologically explored the modulation of the MMN amplitude to an oddball tone by the preceding number of standard tones, showing the expected effect under placebo of an enhanced MMN amplitude when a large number of preceding standards tones had be presented, an effect called MMN memory trace effect (MMN slope). This effect was lost under S-ketamine, but retained under psilocybin. In other words, NMDAR blockade but not the 5-HT_{2A}R system is implicated in PE processing as indexed by the MMN as a form of implicit perceptual learning. Moreover, the processing of PE at baseline, i.e. without any drug intake relates to the extent of S-ketamine-induced cognitive impairments.

A PE reflects the surprise of an unexpected event (Egner et al., 2010). Thus, the frontally generated MMN slope under placebo could also be interpreted in such a way that the occurrence of the deviating tone becomes continuously more surprising with increasing number of preceding standard tones. This increased surprise to the deviant tone is based on suppressed responses to repeated standard tones, i.e. to repetition suppression (RP). The “surprise reduction” to repeated standard tones seen under placebo is lost under S-ketamine. This means that individuals under S-ketamine were not sensitive to contextual factors beyond the physical properties of the stimulus, such as the probability that a repetition will occur, or the relevance of the repeated stimulus to the task at hand. Notably, S-ketamine disrupted only the frontally generated MMN slope but not the temporal one. A similar reduction of the frontal MMN slope was observed in schizophrenic patients (Baldeweg et al., 2004). Our result and the established importance of NMDARs for synaptic plasticity during perceptual learning (Kandel, 2001; Morris et al., 1986) fits well with predictive coding models of the MMN, which suppose a NMDAR-dependent plasticity mechanism. In these theories (Friston, 2005; Stephan et al., 2006), the MMN generates by information passing across different hierarchically organized neuronal ensembles. Within this hierarchy, each level strives to attain a compromise between information about sensory inputs provided by the level below and predictions provided by the level above (Friston, 2005; Rao and Ballard, 1999). A PE emerges when the higher-level predictions (top-down) do not match with the actual sensory input (bottom-up). The general principle of learning is to build flexible models of the environment, which is achieved by minimizing PEs at all levels of the hierarchy. Critically, such a Bayesian passing scheme depends on NMDAR-dependent short-term plasticity, which is critical for adjusting the connection strength of glutamatergic synapses within the hierarchical architecture. Motivated by this theoretical concept, a recent MMN study applied DCM to examine effective connectivity among different brain regions involved in the MMN generation (Garrido et al., 2008). Based on fMRI studies revealing that the MMN propagation involves generators in bilateral A1 and STG, and right IFG (Doeller et al., 2003; Opitz et al., 2002) (Figure 1), the DCM work revealed that the

most plausible mechanism underlying the MMN generation contains changes in coupling within bilateral A1 (post-synaptic modulation), combined with plasticity of inter-areal connections between temporal and frontal regions. Thus, in terms of predictive coding models, the MMN would arise from a failure to predict bottom-up input and suppress the resulting PE (Garrido et al., 2008; Garrido et al., 2009).

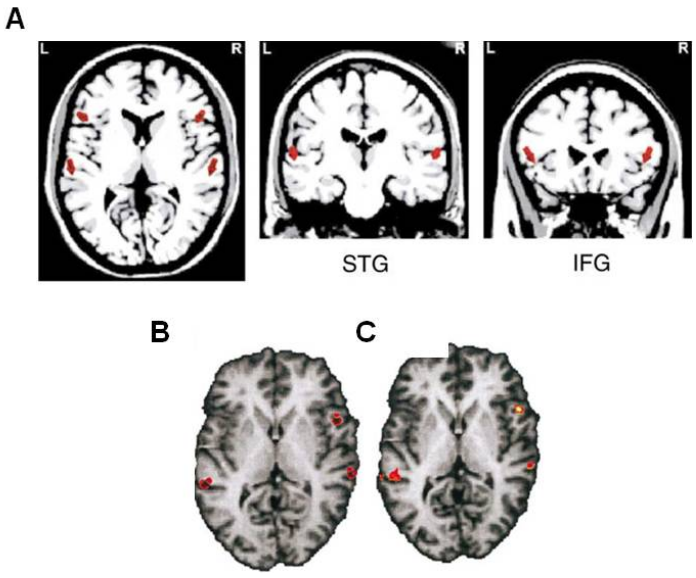

Figure 1 MMN underlying sources revealed by EEG and conjoint EEG and fMRI measures. **A)** Dipoles indicated by red arrows at bilateral STG. **B)** Dipole locations at bilateral STG and right IFG and **C)** significant fMRI activation for deviants. Adapted from Garrido et al. (2009).

According to this, our finding of a reduced frontal MMN memory trace induced by S-ketamine may reflect a drug-induced perturbation of NMDAR-dependent plasticity of temporo-frontal connections (forward) that serves to adjust PE message passing between the STG and the IFG during MMN generation. In other words, the disruption of the frontal MMN by S-ketamine may result from a deficient adjustment of frontally generated predictions about temporal inputs due to insufficient PE-dependent plasticity of forward connections. The plausibility of this potential mechanism was computationally examined in *chapter 3*, which is discussed below.

It remains the question why manipulation of the 5-HT system via psilocybin did not disrupt PE processing in this study, given that modulatory neurotransmitters such as 5-HT are proposed to influence PE processing as well (Corlett et al., 2009) and may be one of the key modulators interacting with NMDARs to produce aberrant synaptic plasticity in schizophrenia (Stephan et al, 2009). The lack of MMN effect following 5-HT manipulation is consistent with previous results (Heekeren et al., 2008; Umbricht et al., 2003). However, these findings do not necessarily contradict with that idea that 5-HT has an effect on PE processing and synaptic plasticity, but rather implies that the role of 5-HT could be expressed in a regionally specific manner, and may thus not be a critical factor in PE processing during the MMN paradigm (cf. Garrido et al, 2009). In this view, it is conceivable that psilocybin will

modulate for example the processing of visual PEs. Alternatively, recent theoretical works suggested crucial differences between PE per se and the precision or uncertainty about those errors (Corlett et al., 2009; Corlett et al., 2011). They propose that fast glutamatergic neurotransmission represents PE and slower neuromodulators encode the precision of PEs. In accordance, optimal inference relies on both the magnitude of PEs and its precision. Consequently, aberrant PE processing did not exclusively mean a fault in the PE magnitude as indexed by the MMN amplitude, but also an estimate of its precision – its uncertainty (Corlett et al., 2009). The size of the PE is meaningless without an estimate of its precision (Fletcher and Frith, 2009). This is different to the effect of S-ketamine here, which records only the magnitude of PEs (MMN amplitude). Although psilocybin did not disrupt the magnitude of PEs with the MMN generation, its influence on the precision of PEs is still unknown. Therefore, implicit perceptual learning as indexed by the MMN amplitude of PEs appeared not to be sensitive to 5-HT_{2A}R manipulations (or to the dose of psilocybin used in this study), but may be alter the precision of PEs (i.e. MMN latency).

Furthermore, we also explored whether S-ketamine- or psilocybin-induced symptoms could be predicted by the MMN slope under placebo. Such an approach based on the assumption that the formation of psychiatric disorders is the result of a genetic predisposition and the exposure to different kind of external stressors (Brown, 2011), and could be useful to test hypotheses about the cognitive and neural bases of specific symptoms (Corlett et al., 2006; Honey et al., 2008; Krystal et al., 2003; Umbricht et al., 2002). In this study, the MMN slope in the absence of any drug predicted NMDAR-mediated cognitive impairments in healthy volunteers. In other words, a poorer learning performance or a disruption of PE processing, expressed as a reduced MMN slope, characterized a constitution that is more sensitive to disruption of the NMDAR system, which in turns might promote the formation of cognitive impairments. But why should the individual MMN slope under placebo predict S-ketamine-induced cognitive impairments rather than other symptoms? This can be explained by the role of NMDARs in synaptic plasticity, which is a crucial mechanism for PE-dependent learning (Stephan et al., 2006; Stephan et al., 2009). A lot of symptoms in schizophrenia including cognitive impairments can result from aberrant synaptic plasticity during perceptual learning. In this view, aberrant synaptic plasticity leads to insufficient PE processing and to inadequate learning, which again results in impairments to adapt one's beliefs and behavior accordingly. Furthermore, the roving MMN paradigm requires the encoding of de novo information of echoic memory traces on a trial-by-trial basis (Baldeweg et al., 2004; Cowan et al., 1993). Therefore, considering the MMN slope as an index of individual capacity of utilizing PEs for adaptive cognition through NMDAR-dependent plasticity, one would predict that the higher this individual capacity in the drug-free state (i.e. the higher the MMN slope under placebo), the less pronounced the effects of S-ketamine on PE-dependent learning and subsequent aberrations in adaptive cognition. This is what we found. However, although in the current study the aberrant PE signal is statistically related to cognitive impairments subsuming items for disordered thought and loss of control over body and thought, we do not preclude associations with others symptoms of psychosis, notably hallucinations, thought disorders or delusions. In this context, closer inspection of the impaired control and cognition subscale provides certain inference relative to abnormal belief formation, because it comprises items like "I felt like a marionette", "I had difficulties in

distinguishing important from unimportant things", "I was not able to complete a thought, my thought repeatedly became disconnected" or "I had the feeling that I no longer had a will of my own." Along this line, abnormal belief formation emerges when predictions are not updated appropriately on the basis of new evidence (Hemsley and Garety, 1986), which nicely corresponds with the disruptions of the MMN slope.

Summarized, our results suggest that the frontal MMN memory trace effect may provide a useful approach to study NMDAR-dependent PE processing during the MMN as a form of implicit perceptual learning, and further provide important insights into the formation of psychosis in general and the emergence of cognitive impairments in particular. Such investigations are of considerable interest, given the potential of the MMN to predict the risk of psychosis (Bodatsch et al., 2010; Orosz et al., 2011; Shaikh et al., 2011) and to distinguish further between first-episode psychosis and individuals at ultra-high risk of psychosis (Atkinson et al., 2011). Furthermore, many atypical antipsychotics were developed on their potential to block the LSD activity at 5-HT_{2A}Rs (Colpaert, 2003), or their development are inspired by NMDAR antagonist models of psychosis (Anand et al., 2000; Deakin et al., 2008; Malhotra et al., 1997; Patil et al., 2007). Under this perspective, we suggest that the assessment of the MMN memory trace effect may also provide a promising tool to evaluate the efficacy of novel glutamatergic-based treatments, which particularly treat cognitive impairments. To conclude, understanding the mechanism of psychedelics provide important insights into the pathophysiology of psychosis, what in turn facilitates the development of better pharmacological therapies for schizophrenia (González-Maeso and Sealfon, 2009).

In my future research, I aim to investigate the role of different pharmacological manipulations on paradigms requiring the processing of PEs using EEG and fMRI analysis in healthy volunteers. The purpose is to understand the role of different neurotransmitters on PE processing (notably magnitude and precision) and its relation to the formation of specific symptoms. The paradigms I will use contain different forms of learning; stimulus-stimulus and stimulus-response associations. The question is whether predictive physiological markers for specific symptom expressions can be identified. For that, different drug model of psychosis are needed, i.e. serotonin, glutamate, dopamine models of psychosis, and tasks requiring specific cognitive challenges, which confer a vulnerability to associated symptoms. Briefly, we search robust paradigms to challenge defined cognitive processes linked to specific symptoms for different drug-induced psychosis. For example, a failure of self-monitoring may lead to the emergence of auditory hallucinations linked to an increased activity in the frontal and temporal cortex (McGuire et al., 1995). Thus, we need self-monitoring task to examine whether the evoked signal in frontal and temporal brain regions is associated with auditory alterations induced by a specific pharmacological agent. Notably, to ensure compelling consistency between task, region-specific signal and symptom, dose-dependent drug-models are requested. A further step will be to translate these models into patient studies. Keeping in mind that the MMN appears to distinguish between individual at ultra-high risk of developing schizophrenia and individuals in the first episode of a psychosis (Atkinson et al., 2011), a task-specific physiological signal may not only offer the possibility to predict specific symptoms, which are robustly associated with a certain pharmacology,

but might also lead to some inference about the disease progress. At best, we have brain marker of the prodrome. Finally, such kind of works may provide useful evidence to develop early intervention strategies to treat an individual pattern of symptoms. In consideration of predictive coding models, we may have a concept to examine psychosis translational. Indeed, both the susceptibility to psychosis and the responses to drugs are influenced by individual's genetic variability. In addition, environmental factors, such as prenatal exposure to infection (Brown, 2006) and social disadvantage (van Os et al., 2005) do also contribute to psychosis. Furthermore, psychological factors like suggestibility or absorption should be considered as well, because these factors interact on the one hand with drug-induced symptoms, and on the other hand with the susceptibility to hypnosis (Braffman and Kirsch, 1999), which recently served as model of psychosis (Barnier et al., 2008; Corlett et al., 2011). Thus, the Bayesian model of psychosis allows us to consider the interaction between biological and environmental factors, which are relevant to schizophrenia.

Discussion of Chapter 3

In *chapter 2,* we have interpreted the MMN and the effect of the NMDAR antagonist S-ketamine on it under the perspective of predictive coding models. Figure 2 depicted a simplified schema of the MMN generation within the framework of predictive coding. Although the Bayesian way of thinking provides us some possible explanations about the NMDAR-mediated disruption of the MMN, however, it has not yet been revealed whether a failure in bottom-up error propagation upwards the neural hierarchy or a defect in the top-down inference mechanism downwards the hierarchy reflects the core of the problem. What we need to disentangle this question is to compute the effect of S-ketamine on effective connectivity within the network underlying the MMN generation. This was exactly the purpose of the study outlined in *chapter 3*.

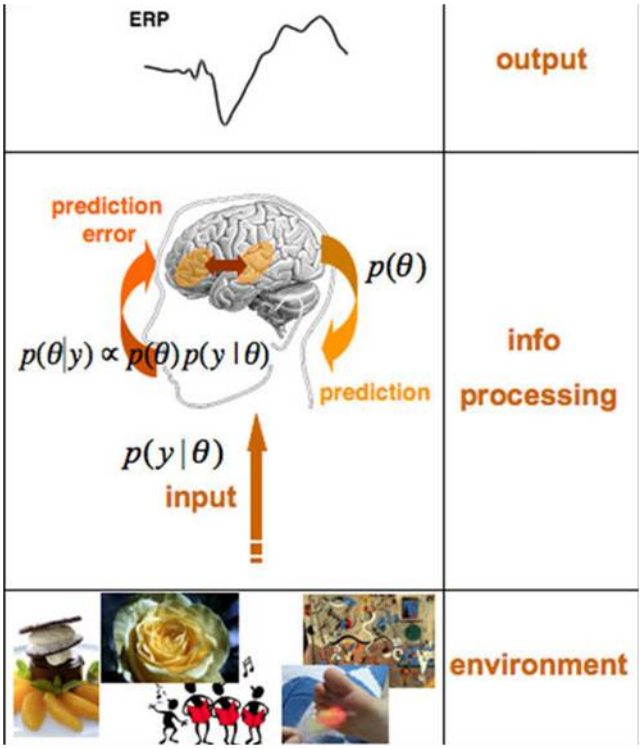

Figure 2 The MMN interpreted in terms of predictive coding. Illustrative scheme of the general framework of hierarchical Bayes and predictive coding as an explanation for ERP emerge. Adapted from Garrido et al. (2009).

The hierarchical neuronal architecture underlying the generation of the MMN was established using DCM (Garrido et al., 2008). DCM revealed that the MMN is generated by self-organized interactions within a hierarchy of cortical sources comprising bilateral A1 and STG and right IFG. This model involves local post-synaptic adaptation within the A1 and temporo-frontal interaction between different auditory systems (Figure 3). Computationally, this synaptic adjustment is driven by the magnitude of

trial-wise PEs in lower-level structures, leading to adjustment of predictions generated by higher-level structures.

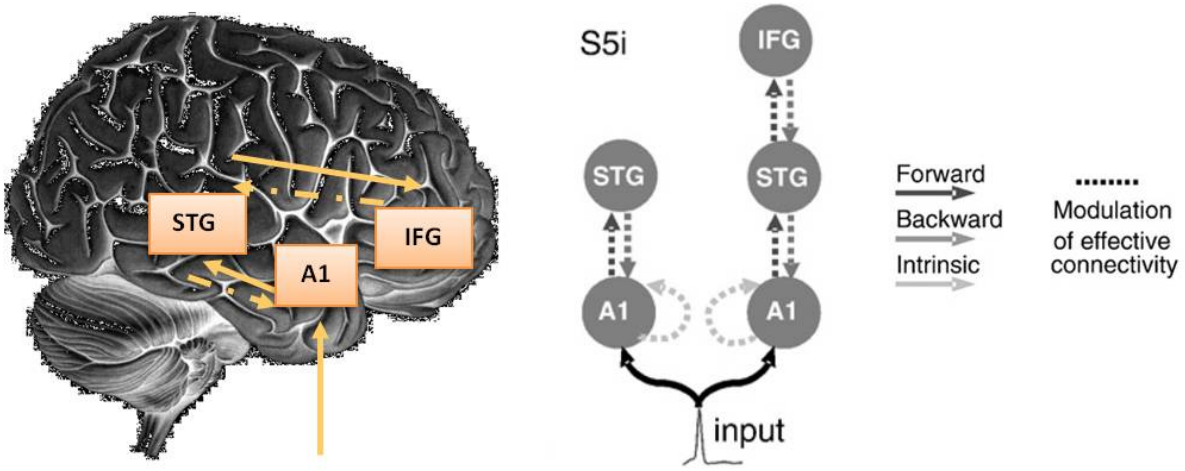

Figure 3 Hierarchical network underlying the MMN generation, comprising five interconnected cortical areas; allowing for local adaptation within primary auditory cortices and plastic changes in extrinsic connections. Adapted from Garrido et al. (2008).

In keeping with that, we have already hypothesized in *chapter 2* that our finding of a reduced MMN following S-ketamine administration may reflect a drug-induced perturbation of NMDAR-dependent plasticity of temporo-frontal connections (forward) that serves to adjust PE message passing between the STG and the IFG during the MMN generation. Here, we have computationally examined this hypothesis by combining statistical parametric mapping (SPM) with DCM modeling of ERP data (David et al., 2006; Friston et al., 2003). Specifically, using SPM and DCM had three parts: (i) confirmation that there is a significant mismatch response (i.e. MMN) between the first and the sixth tone in the placebo and drug conditions, i.e. to replicate our previous ERP analysis (Schmidt et al., 2011), (ii) hypothesis or model testing to examine whether the MMN response is mediated by changes in intrinsic and extrinsic connectivity, i.e. to replicate the initial DCM analysis on MMN data (Garrido et al., 2008), and most important (iii) quantitative connectivity analysis to determine the coupling parameters, which significantly distinguished between the placebo and S-ketamine condition and also predicted psychotic symptom formation following S-ketamine administration.

Briefly summarized, our results revealed a significant MMN response over frontal electrodes in both the placebo and S-ketamine condition, consistent with our previous results (Schmidt et al., 2011). It is important to note that the MMN response was significantly attenuated in the S-ketamine compared to the placebo condition, which also corresponds with our previous finding. Furthermore, DCM connectivity analysis of the MMN response revealed that the model with modulation of forward and backward connections, as well as post-synaptic modulation had the largest model evidence. This suggested that the model that fit the data best also represented specific mechanistic hypotheses

about the MMN generation, including predictive coding and adaptation, which is in accordance with previous DCM results (Garrido et al., 2008). In addition, random effects family-level analysis showed that adaptation models, which assessed whether the amplitude differences between the standard and deviant tones were driven by post-synaptic modulations, best explained the MMN responses in both placebo and S-ketamine conditions. Most intriguingly, by examining the neuromodulatory effect of S-ketamine on effective connectivity, a significant reduction in effective connectivity following S-ketamine administration was observed in the forward connection from the left A1 to the left STG. Moreover, we found that this reduction in bottom-up effective connectivity predicted significant S-ketamine-induced cognitive impairments. In what follows, I extend the discussion of *chapter 3* by embedding and comparing our findings also in the context of an alternative concept instead of Bayesian concepts and by providing possible future direction for this field.

According to the disconnection hypothesis of schizophrenia (Friston, 1998; Stephan et al., 2006; Stephan et al., 2009), disordered brain connectivity is thought to be a central pathophysiological feature of schizophrenia. This hypothesis was motivated by initial positron emission tomography (PET) studies revealing abnormal connectivity between frontal and temporal lobe regions in schizophrenia (Friston, 1998; Friston and Frith, 1995; Frith et al., 1995), which was recently supported by fMRI works in schizophrenia patients (Calhoun et al., 2009; Pettersson-Yeo et al., 2011). However, the pharmacological mechanism underlying this failure of integration and its significance for illness symptoms has not yet been experimentally investigated. We provide empirical evidence that the blockade of the NMDAR system leads to dysfunctional fronto-temporal integration within the hierarchical network underlying the MMN generation due to deficient bottom-up effective connectivity, which extent was further correlated with S-ketamine-induced cognitive impairments. The relation between aberrant functional integration and the emergence of cognitive impairments can be understood by considering cognitive symptoms in schizophrenia such as thought disorders as instances of NMDAR-mediated disruption of synaptic plasticity, which leads to dysfunctional perceptual learning and inferences (Friston, 2005; Friston, 1998). In other words, cognitive impairments result from impaired perceptual learning and inferences. Thus, various cognitive or negative symptoms frequently seen in schizophrenia, if not all of them, can be understood as deficits in different forms of learning and memory (Stephan et al., 2009). For example, one of the cardinal cognitive dysfunction associated with schizophrenia is a working memory deficit (Goldman-Rakic, 1994), which describes a deficit in the short-term storage of salient information in a limited capacity storage system in service of behavior (Baddeley, 1981). In this view, working memory processes account that behavior, thought and percepts are constrained to what is appropriate to the current situation (Barch et al., 2001; Braver et al., 1999). As a consequence, working memory deficits disturb contextual appropriateness (Barch et al., 2003) and the ability to logically order thought and produce coherent and communicative speech. In accordance, it has frequently been reported that abnormal fronto-temporal connectivity in schizophrenia is associated with cognitive impairments as expressed by working memory deficits (Allen et al., 2008b; Allen et al., 2010; Crossley et al., 2009; Fusar-Poli et al., 2010; Meyer-Lindenberg et al., 2001; Wolf et al., 2007; Wolf et al., 2009), which can manifest clinically as thought disorders (Kircher et al., 2001; Leube et al., 2008). Similar to these aberrant

pattern activations in schizophrenia patients, ketamine also altered the activity in fronto-temporal regions associated with thought disorders (Nagels et al., 2011a; Nagels et al., 2011b). Moreover, the level of frontal and temporal activation during task performance was predictive of thought disorder experienced under ketamine (Honey et al., 2008). Most important in the context of this work, schizophrenia patients do also show aberrant fronto-temporal coupling during the MMN generation as evidenced by impaired frontal but not temporal MMN components (Baldeweg et al., 2002; Baldeweg et al., 2004; Sato et al., 2003). Moreover, the extent of the frontal MMN deficit was related to the severity of cognitive impairments (Baldeweg et al., 2004). The relation between the MMN deficit and cognitive impairments in schizophrenia patients correspond precisely with our S-ketamine results. Moreover, by using computational modeling we further showed that the relation between cognition and MMN is based on NMDAR-mediated dysfunctional integration between temporal and frontal brain regions. Given that abnormal fronto-temporal connectivity is associated with working memory deficits (i.e. cognitive impairments) in schizophrenia (Crossley et al., 2009; Fusar-Poli et al., 2010) and in S-ketamine treated individuals (Nagels et al., 2011a; Nagels et al., 2011b) and that the generation of the MMN requires echoic memory capacity, one would predict that the extent of fronto-temporal dysconnectivity within the MMN network correlate with cognitive impairments in schizophrenia and ketamine-induced cognitive impairments. That is precisely what previous studies and we found. We suggest that schizophrenic patients and individuals under S-ketamine are not sensitive to contextual factors beyond the physical properties of the stimulus, thereby loosing the ability to predict forthcoming events and in consequence exhibit aberrant sensitivity to surprising and salient events. In this way, the world of schizophrenic patients and individuals administrated with NMDAR antagonists becomes highly unpredictable, different things seem important, and important things seem different (Corlett et al., 2007), i.e. they build false models of the world. If one assumes that S-ketamine-induced cognitive impairments resemble those of schizophrenia, we suggest that the impaired frontal MMN component in schizophrenia is based on deficient top-down prediction about the temporal input as a result of a reduced NMDAR-mediated bottom-up input from the temporal auditory brain system. However, to fully confirm the disconnection hypothesis, patient studies using MMN paradigms in combination with DCM are needed.

Previous hypothetical reflections proposed that in general higher levels of the neuronal hierarchy specify top-down predictions via NMDAR signaling, while any mismatches between expectancy and experience (i.e. PE) are conveyed upwards through the hierarchy via rapid AMPA and GABA receptor signalling (Corlett et al., 2009; Corlett et al., 2011; Friston, 2005). Specifically, it has been postulated that S-ketamine attains its effect on the one hand over increased random spiking mediated by AMPAR up-regulation and GABA receptor signalling, which leads to perturbation of feed-forward processing and further over a NMDAR-mediated decrease in burst firing, which should affect specification of prior expectation (top-down prediction) (Corlett et al., 2009). To put this more simply, they proposed that ketamine disturbs fast feed-forward mechanism (PE signal) through AMPA up-regulation and GABA receptor signalling and slow feedback constraint (priors) through NMDA blockade. In this study, we experimentally revealed that S-ketamine did not perturb top-down action within the network underlying the MMN, in contrast to the proposed model. Furthermore, although S-ketamine indeed disturbed

feed-forward connections in this study consistent with the theoretical model, whether our finding of a NMDAR-mediated perturbation of bottom-up processing is due to AMPA up-regulation, GABA receptor signaling or NMDAR blockade per se is hard to derive from our data. However, previous evidence in fact revealed that abnormalities of GABAergic function in schizophrenia may result from NMDAR dysfunction (Laruelle et al., 2005) and that the interaction between both neurotransmitter systems critically contributes to cortical plasticity (Kubota and Kitajima, 2010) with highly relevance for schizophrenia (Frankle et al., 2003), which is in line with the proposed model. In this view, a very recent study demonstrated that baclofen, which targets GABAergic neurons, facilitates reinforcement learning via increased stimulus-response associations (Terrier et al., 2011), suggesting that GABA receptor signaling alters the connection strengths within the hierarchical network underlying reinforcement learning. Thus, in a future study, we intend to partly disentangle this open question by investigating the role of different doses of baclofen on effective connectivity during stimulus-stimulus learning (MMN generation). In regard to the proposed model, we are particularly interested in how baclofen affects bottom-up effective connectivity. Based on the fact that baclofen primarily acts as $GABA_B$-receptor agonist, one could hypothesize a net GABAergic inhibition with a concomitant increase in the MMN amplitude via less restrained NMDA-receptor plasticity. On the other hand, high doses (e.g. 100 mg of baclofen) would exert the opposite effect, given that high-dose baclofen not only targets GABAergic interneuron's but also other transmitter systems.

It has been suggested that deficits in early sensory processing may explain the observed MMN reduction in schizophrenia patients (Javitt, 2009; Leitman et al., 2010). These bottom-up models suggest that NMDAR-mediated deficits in early sensory processing contribute to cognitive impairments in schizophrenia (Javitt, 2009). This concept is supported by patient studies in which the latencies of the MMN amplitude and the later P300 increases in parallel, suggesting significant contributions of early sensory processing dysfunction to higher-order cognitive impairments (Leitman et al., 2010), given that they assume that the MMN exclusively represents feed-forward low-level processing and that the P300 appears to represent activation of higher-level circuits with the goal of determining the higher-level significance of the fact that an unexpected event has just occurred. We partly agree with these inferences, but allude that the MMN generation in fact involves both temporal and frontal generators (Doeller et al., 2003; Grau et al., 2007; Opitz et al., 2002; Rinne et al., 2000), which reveal intra- and inter-areal interactions (Garrido et al., 2008). Regarding the MMN under the framework of predictive coding models (Garrido et al., 2009), the frontal MMN component represents the high-order neuronal system, while the temporal MMN component is at the bottom of the hierarchy. In this view, our finding that NMDAR-mediated perturbation of bottom-up effective connectivity leads to cognitive impairments corresponds with these bottom-up models insofar that indeed cognitive impairments are might triggered by NMDAR-mediated deficits in bottom-up processing, but importantly, that must not necessary imply preserved top-down processes. Notably, in this study we computed effective connectivity underlying the generation of single MMN amplitudes independent of the previous context, i.e. without parametric modulation of the number of preceding standard tones (no memory trace). Given that the MMN memory trace effect is entirely due to learning and cannot result from differential states of frequency-specific auditory neurons in the temporal cortex, it seems unlikely that a pure

deficit in early sensory processing could account for the reported S-ketamine-induced disruption of the MMN memory trace effect, i.e. for the S-ketamine-induced cognitive impairments (Schmidt et al., 2011). We will examine the neuromodulatory effect of S-ketamine on effective connectivity during the generation of the MMN memory trace effect, i.e. parametric modulation of the number of preceding standard tones in future modeling studies. Along this line, previous evidence revealed that early ERPs have been associated with bottom-up effects, while later components have been ascribed to endogenous dynamic involving top-down influences (Schiff et al., 2006). Although, at least in my opinion, bottom-up and top-down processing always reflect parallel processes, it has been demonstrated by using DCM that top-down prediction are specifically necessary to explain later ERPs (Garrido et al., 2007a). Along this line, the generation of the MMN involves both bottom-up and top-down processing and we showed that S-ketamine disrupted bottom-up processing of PEs, while top-down processing remained unaffected. Theoretically, these PEs require higher levels of the hierarchy to minimize them. However, as the errors are false as in the S-ketamine case here, these adjustments can never fully resolve the problem. As a result, PEs will be propagated even further up the system to ever-higher levels of abstraction. The severity of the insult to the Bayesian system may account for how far up in the hierarchy a false PE will go (Fletcher and Frith, 2009). This means that false upwards propagated PEs will consequently lead to false predictions about the incoming input as well in dependence of how high in the hierarchical level we are. Under this perspective, although we found no aberrant top-down prediction following S-ketamine within the MMN network, however, we suggest that in later ERPs involving more top-down control than the MMN, the S-ketamine-induced reduction of bottom-up processing would in consequence also affect top-down predictions, what would speak against bottom-up models of cognitive impairments in schizophrenia. Thus, actually I'm computing DCMs with time ranges from 0-400 ms post-stimulus instead of 0-250 ms to account also for the later P300 ERP. We propose that the S-ketamine-induced deficit in bottom-up processing of PEs might lead as a consequence to aberrant top-down predictions from the time frame of the P300 ERP.

However, many questions about the role of synaptic plasticity in the pathophysiology of schizophrenia remain. As Harrison and Weinberger already proposed (2005), " ... it will not be synapses per se but the neural circuits in which they participate which will prove to be the appropriate explanatory level to understand how the genetic influences operate ... various combinations of susceptibility genes can converge on synaptic processing in these microcircuits to effect a common pattern of dysfunction and emergent symptoms, though the specific combination of genes and possibly alleles can vary across ill individuals." Along this line, susceptibility genes in the case of schizophrenia have been well characterized and significant convergence on glutamatergic pathways is observed (Allen et al., 2008a; Walsh et al., 2008) (Table 1). For example, the glutamate-related genes NRG1 and DTNBP1 are involved in both building of long-range connections during development and in regulating synaptic plasticity (Harrison and Weinberger, 2005). This is important, because any impairment in synaptic plasticity would affect the way long-range connections are established in the developing brain, given that the strength of functional coupling between two neurons determines whether their connection survives developmental pruning (Hua and Smith, 2004). Therefore, we have to identify glutamatergic susceptibility genes, which alter synaptic plasticity responsible for the connectivity of specific brain

systems underlying the formation of psychotic symptoms. This knowledge should be considered in computational models of learning (DCMs) to understand the consequence and loci of abnormal plasticity processes.

Table 1 Glutamate- and non-glutamate-related genes implicated in schizophrenia. Adapted from Javitt (2011).

Glutamate-related genes	Dopamine-related genes	Other
NMDAR *(GRIN2B)*	Catechol-O-methyltransferase *(COMT)*	GABA *(GABRB2)*
Serine racemase *(SRR)*	Dopamine receptor type 1,2, 4 *(DRD1, DRD2,DRD4)*	5-HT *(SLC6A4, TPH1)*
D-Amino acid oxidase *(DAO)*		Inflammatory *(IL1BMHC))*
D-Amino acid oxidase activator *(DAOA, G72)*		Folate *(MTHFR)*
Dysbindin *(DTNBP1)*		Haptoblobin *(HP)*
Neuregulin *(NRG1, ERBB4)*		axon guidance *(PLXNA2)*
Neurogranin *(NRGN)*		Adoptosis *(TP53)*
mGluR7 *(GRIM7)*		transcription *(TCF4)*
EAAT1 *(SLCA13)*		Unknown *(ZNF804A)*

Another opportunity to complement the analysis from the present study is to employ recently developed computational models, which use the same Bayesian inference framework as DCM but are agnostic about physiological mechanisms. Instead, they enable the investigation of trial-by-trial changes in MMN amplitude from a purely computational (information theoretic) perspective. In other words, they help clarifying which computational quantities (e.g., prediction errors or surprise) are reflected by the trial-by-trial dynamics of MMN expression (Lieder et al., in preparation). These models, once they are fully established, should enable us to examine the effects of ketamine on MMN generation from a complementary perspective.

Finally, there is evidence to suggest that illness onset is associated with exacerbation of less severe fronto-temporal dysfunctional connectivity seen in those vulnerable to those with psychosis. Crossley and colleagues (2009) demonstrated a progressive increase in dysfunctional fronto-temporal connectivity during a working memory task from healthy controls to subjects with an at risk mental state (UHR) and further to individuals with first psychotic episode (FEP). Supportive for that, the at-risk mental state is associated with abnormalities of regional brain function that are qualitatively similar to, but less severe than, those in patients who have recently presented with psychosis (Broome et al., 2009). This is in line with recent studies revealing that the assessment of the MMN may allow distinguishing between UHR and FEP (Atkinson et al., 2011; Bodatsch et al., 2010; Orosz et al., 2011; Shaikh et al., 2011; Shin et al., 2009). Regarding the MMN as echoic working memory, it is conceivable that this differentiation between UHR and FED by means of the extent of MMN reduction is due to the extent of fronto-temporal dysconnectivity. Therefore, the assessment of the MMN in combination with DCM might allow distinguishing between “ultra-high risk” and first-episode psychosis on the basis of dysfunctional fronto-temporal connections. Hence, our findings not only demonstrate that DCM in combination with neurophysiological measures and pharmacological manipulations

provides a promising framework to identify and understand further the role of different neurotransmitters in neuronal plasticity and but also that the combination of MMN and DCM may help us to develop diagnostic markers (biomarkers) to subdivide schizophrenic patients into physiologically defined groups on the basis of their NMDAR-mediated fronto-temporal dysconnectivity. In consequence, such an approach may promote the detection of early cognitive impairments, which in turns leads to valuable predictions either about the illness progress or about reasonable pharmacological treatments.

5.2. The Role of Glutamate and Serotonin in Emotional Processing

Discussion of Chapter 4

Recent evidence show that psychedelics modulate neural circuits that have been implicated in affective disorders, and can ameliorate clinical symptoms of such disorders (Vollenweider and Kometer, 2010). Indeed, it has been shown that acute administration of the NMDAR antagonist ketamine ameliorates depressive symptoms in treatment-resistant depression within a few hours persisting for several days (Diazgranados et al., 2010; Zarate et al., 2006), while acute administration of the mixed 5-HT receptor agonist psilocybin in healthy subjects leads to heightened mood, increased emotional excitation and sensitivity (Studerus et al., 2010) and decreases anxiety in terminal cancer patients within a month (Grob et al., 2011). However, although recent studies revealed exciting new insights about the underlying molecular mechanism of ketamine's rapid antidepressant effect (Autry et al., 2011; Duman et al., 2012; Li et al., 2010) (Figure 2) and of psilocybin's mood enhancing effect (Vollenweider and Kometer, 2010), the understanding how ketamine and psilocybin acutely modulate the processing of emotional stimuli, which requires functional integration within a specific network, is far from complete.

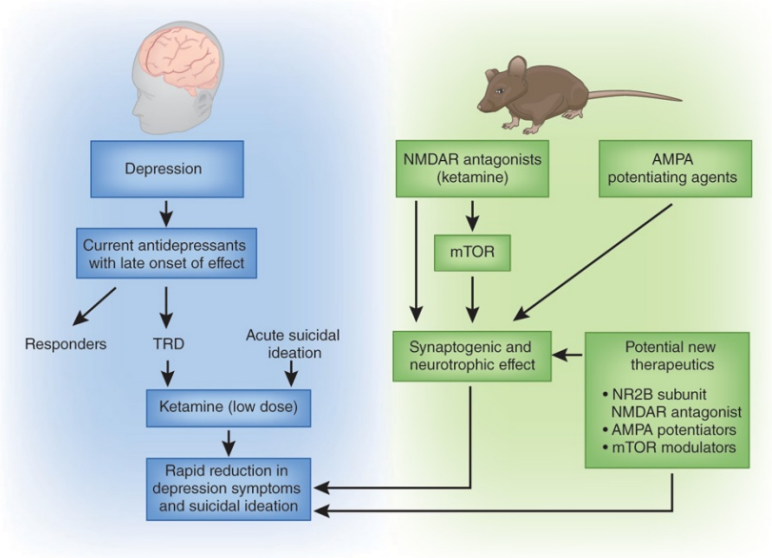

Figure 2 Translational overview of ketamine's rapid antidepressant effect and the potential role of synaptogenic and neurotrophic mechanisms in depression. Adapted from Murrough & Charney (2010).

To investigate further the neuronal underpinnings of the effect of psilocybin and S-ketamine on emotional processing, in this study here, we elucidated first whether psilocybin and S-ketamine affect emotional face processing in a valence specific manner. We selected faces due to the fact that the recognition of other people's emotion from their facial expressions is fundamental to social interaction and behavior of human beings. Furthermore, because negative processing biases in depression may result not only from biased cognitive appraisal, but also from automatic processing biases that

influence the access of sensory information to awareness (Suslow et al. 2010, Victor et al. 2010), we second investigated whether both drug effects on emotional face processing vary as a function of visual awareness. Given that accumulating evidence recommended the use of ketamine to treat depression, we took ketamine as proof-of-concept agent to physiologically assess the plausibility of an alternative medical agent to treat affective disorders, namely the mixed 5-HT receptor agonist psilocybin. The following discussion should be read with this background in mind. Specifically, we have investigated how early visually evoked responses to emotional facial expressions during non-conscious compared to conscious processing are modulated by S-ketamine or psilocybin. Notably, visual responses to emotional stimuli are believed to reflect regulation of basic emotional signals associated with social cognition (Schultz et al., 2003; Singer et al., 2004). Our data revealed that both psilocybin and S-ketamine reduced early visual responses to fearful faces as expressed by a reduced N170 ERP response, whereas N170 ERP responses to happy faces were reduced exclusively by S-ketamine. Furthermore, the S-ketamine- and psilocybin-induced reduction of the N170 ERP response to facial expressions was more pronounced during conscious compared to non-conscious processing, irrespective of facial valence. In the following, I extend the discussion section of chapter 4 by adding some new points concerning the neurobiological mechanism underlying on the one hand the N170 ERP reduction in response to fearful faces induced by both drugs and on the other hand the dissociable effects of psilocybin and S-ketamine on the N170 ERP in response to happy faces. Finally and based on these points I provide possible research strategies for this field.

According to several source modeling studies (Deffke et al., 2007; Rossion et al., 2003; Sadeh et al., 2010), the generators of the N170 ERP have been localized to the FG, which encodes the structural configuration of facial features. Since EEG sensor signals result from a mixture of neuronal sources, one should be cautious about relating our findings to neural sources in specific locations. In other words, the N170 ERP must not necessarily correspond to the FG. Nevertheless, the increased visual response to relevant emotional expressions is likely mediated via rich interconnections between the FG and the amydgala (Amaral et al., 2003; Freese and Amaral, 2005), the coupling of which is additionally strengthened during attentive viewing of emotional faces (Fairhall and Ishai, 2007; Herrington et al., 2011) (Figure 3).

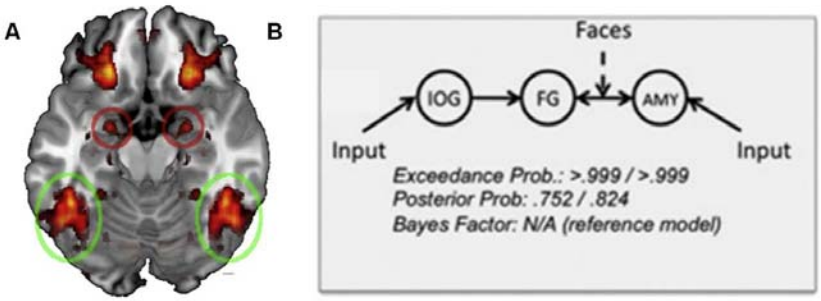

Figure 3 A) Per-voxel tests of faces greater than houses. Circles highlight regions from which ROIs were extracted for connectivity analyses (FG = green; amygdala = red). **B)** Increased effective connectivity between FG and amygdala during face processing. Adapted from Herrington et al. (2011).

Furthermore, emotional face processing does also involve the PFC, which is effectively connected with the amygdala and the FG (Dima et al., 2011). This means that not only the FG and the amygdala are bi-directionally connected during emotional face processing, but also the amydgala and the PFC, as well as the FG and the PFC. Along this line, both S-ketamine and psilocybin were found to deactivate the amygdala and to increase prefrontal neural activity (Vollenweider and Kometer, 2010). Therefore, we suggest that the N170 ERP reduction by both drugs in response to fearful faces is due to altered PFC-limbic coupling induced by both psilocybin and S-ketamine. Moreover, both drugs also enhance extracellular glutamate release into the PFC (Kargieman et al., 2007), which might be responsible for this altered PFC-limbic interplay. This fits well with the finding that abnormal glutamate levels have been identified in various brain regions of depressed subjects (Sanacora et al., 2008) and also with the finding that depressed patients show reduced PFC-limbic connectivity (Dannlowski et al., 2009). Glutamate as the driving force for modulating PFC-limbic circuits is supported by the evidence that various antidepressant drugs with different primary mechanisms (fluoxetine, reboxetine, desipramine) target the glutamatergic system, raising the possibility that glutamate blockade could be a shared mechanism of antidepressant action, along with serotonin reuptake inhibitors (Bonanno et al., 2005).

However, it remains unclear why S-ketamine but not psilocybin reduced the N170 ERP in response to happy faces. In contrast to the processing of negative material, the processing of positive information involves structures, which are associated with reward and motivation including the ventral striatum and the orbitofrontal cortex (OFC) (Ishai, 2007). Imaging studies have demonstrated that the ventral striatum is recruited by the rewarding properties of happy faces (Monk et al., 2008; Phan et al., 2002), and show increased connectivity with the hippocampus during the processing of happy faces (Satterthwaite et al., 2011). Furthermore, the hippocampus and the OFC are also significant correlated for positive faces (Tsukiura and Cabeza, 2011). Keeping this network in mind, the processing of happy faces could be related to the encoding of value-prediction codes that are relevant for the subsequent recognition in memory. The expectations about potential reward likely promote motivation to learn and encode reward-associated faces (Berridge and Robinson, 2003). Such reward-related processes interact with structural encoding processes as indexed by the N170 ERP. Indeed, a recent study revealed that the N170 ERP showed reward-related effects (Marini et al., 2011), suggesting an electrophysiological predictor of a successful encoding into long-term memory, which relies on the hippocampus. In accordance, it has been shown that the FG was positively correlated with hippocampal activation during the successful encoding of faces with high confidence (Tsukiura and Cabeza, 2011). Thus, it is conceivable that S-ketamine and psilocybin differentially modulate reward-related networks, leading to differential N170 ERP responses to happy faces. Noteworthy, rewarding signals are conveyed via dopaminergic neurons (Enomoto et al., 2011; Koob and Le Moal, 2001) and both S-ketamine and psilocybin exhibit affinity for $DA_{1/2}$ receptors (Vollenweider and Geyer, 2001). Hence, varying modulation of the dopamine system in reward regions induced by S-ketamine and psilocybin might also contribute to this dissociable effect on happy face processing.

Yet, the N170 ERP modulation produced by psilocybin and S-ketamine might not only depend on alterations in structures related to emotional processing, but also on alterations in the visual system

per se. In particular, the parvocellular visual system is specialized for fine-grained analysis of object identification by the ventral visual stream, also known as “what pathway” (Foxe et al., 2005; Sehatpour et al., 2010). This corresponds well with the configurationally encoding of faces as reflected by the N170 ERP generated in the FG, which belongs to the ventral stream (Teipel et al., 2007). Thus, it could be hypothesized that the N170 ERP modulation by both drugs is probably followed by alteration in the parvocellular stream. Finally and especially because of the valence-specific effects, the N170 ERP modulation by both drugs is probably an interaction between alterations in structures responsible for both visual (ventral stream) and emotional processing.

In conclusion, our findings suggest that glutamate and serotonin differentially contribute to the modulation of visual responses to emotional facial expressions in healthy humans. The assessment of early visual responses to emotional expressions may provide a useful framework to detect pharmacologically induced changes in emotional processing and might also lead to a greater understanding of pharmacological mechanisms underlying emotional processing biases and its dysfunction in affective disorders. Furthermore, we demonstrated that psilocybin probably offers a promising alternative agent to S-ketamine for the treatment of affective disorders insofar that psilocybin does not alter the processing of happy faces, and further because psilocybin relative to S-ketamine produces more bliss, less depersonalization, and also less cognitive deficits (Vollenweider and Kometer, 2010).

To further examine task-specific functional integration following S-ketamine and psilocybin administration, we intend to translate a similar emotional paradigm into an fMRI study. We are specifically interested in the pharmacologically induced alteration in PFC regions including the anterior cingulated cortex (ACC), dorsolateral PFC (DLPFC) and lateral ventral PFC (VPFC), subcortical regions subsuming the amygdala and striatal structures, as well as visual regions such as the inferior occipital gyrus (IOG), the FG and the superior temporal sulcus (STS). Following this, we will use DCM modeling to estimate effective connectivity within the outlined network and its modulation after drug administration (see Figure 4). Such analyses allow us to better understand functional integration during facial processing per se and the impact of glutamatergic and serotonergic manipulations on it. To further prove the plausibility of psilocybin as an agent to reduce specific symptoms of affective disorders, further studies are needed to examine, on the one hand, whether repeated doses in healthy humans trigger sustained effects in emotional processing, and on the other hand to translate this model into studies of patients suffering from mood or anxiety disorders. We would hypothesized that patients will reveal an aberrant coupling between prefrontal and limbic brain regions due to an attenuated frontal top-down control over limbic structures and that both drugs have the potential to restore an adequate balance between these both regions. Thus, on the long-term, the DCM analysis might give us the opportunity to detect aberrant coupling indicating dysfunctional emotional processing biases, which contribute to vulnerability to mood disorders, and further to examine whether psilocybin and S-ketamine can resist this dysfunctional emotional biases. As it has currently been done to predict the behavioral antidepressant effect of ketamine with different methodological approaches (Salvadore et al., 2009; Salvadore et al., 2010; Salvadore et al., 2011), the use of DCM may serve as promising tool to predict not only susceptibility to mood disorders or even the presence of mood disorders, but

also to predict the effect of potential therapeutic agents on functional integration. What then remains is the relationship to the subjectively perceived mood.

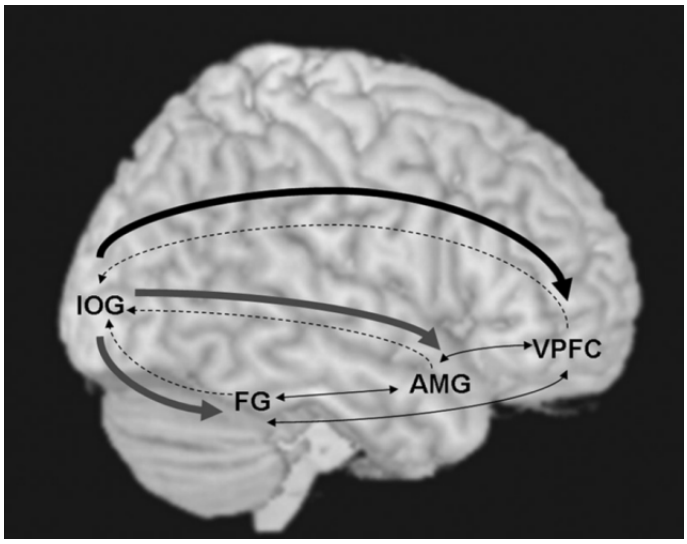

Figure 4 Alterations in effective connectivity within the face-processing network. Thick gray arrows indicate significant endogenous connections and the thick black arrow indicates a significant endogenous connection significantly modulated by anger. Dashed arrows indicate backwards connections and thin black arrows indicate bidirectional connections. Adapted from Dima et al. (2011).

5.3. MMN and N170 Event-related Potentials Under the View of Predictive Coding

To bridge the gap between *chaper 2/3* and *chapter 4*, I show in the next section how our N170 ERP findings can also be interpreted within the framework of predictive coding models. Roughly reviewed, the concept of predictive coding assumes that every neuronal system forms predictions about the upcoming input from a lower-level system based on previous experience. The role of PEs has been classically investigated in reinforcement learning (stimulus-response learning), but recent studies revealed evidence for the processing PEs during stimulus-stimulus learning. In particular, the MMN constitutes an empirical example that PEs may be equally important during perceptual learning of stimulus-stimulus associations that are behaviorally irrelevant instead of stimulus-response relationships, which are of high biological relevance. This entails adjustments to our internal model of the environment so that potentially surprising events can be predicted (den Ouden et al., 2009). MMN theories, which proposed the MMN as a paradigmatic example of learning based predictive coding (Baldeweg, 2006; Friston, 2005), were supported by DCM studies (David et al., 2006; Garrido et al., 2007b). They revealed that the MMN can be understood as PE signal, which results from deviant-induced changes in inter-regional connections strength among the hierarchical network, which in turns depends on NMDAR functioning. Interestingly, such statistical relationships between different stimuli (stimulus-stimulus) to optimize learning are also formed within the visual system. The pioneer work of Rao and Ballard (1999) firstly described that visual processing rests upon feedback connections from higher- to lower-order visual cortical areas, which again carry predictions from lower-level neural activities. Within this hierarchy, representational neurons (R units) form expectations about the physical identity of a stimulus and send the expectations further to next lower level (E unit). The neurons in the E unit encode the PE when the expected information do not match with the actual input, and pass this PE back to the R unit neurons to update their predictions (Figure 7). In other words, predictive coding propose that perceptual inference proceeds as an iterative matching process of top-down predictions against bottom-up evidence along the visual cortical hierarchy (Friston, 2005; Rao and Ballard, 1999).

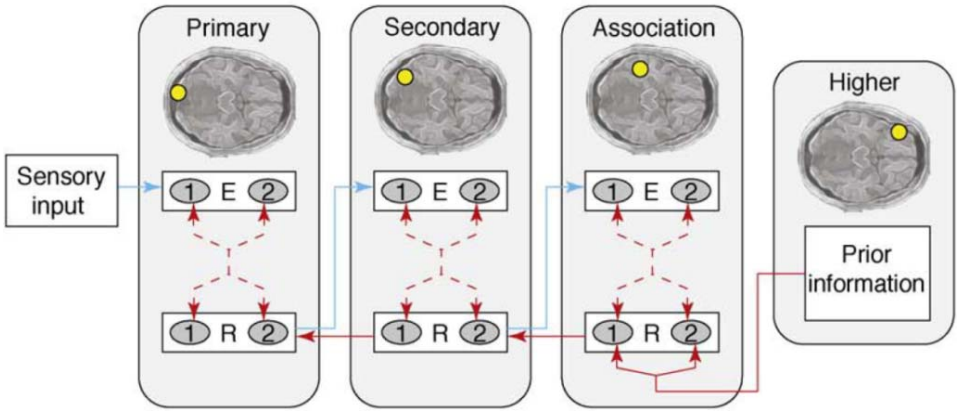

Figure 7 Predictive coding in visual perception. In this scheme, representation units (R) encode expectations about next incoming information and error units (E) encode the PE between the

prediction and the observed input to update the prediction in the R neurons, i.e. predictions are used as priors for the preceding layer. Adapted from Summerfield and Egner (2009).

A very recent study suggests that even early visual activity can be modulated by learning, suggesting top-down predictions (Rauss et al., 2011). The authors argued that these early top-down effects on visual processing can be regarded as a consequence of predictive coding mechanisms in the visual system. Low-level visual areas might adapt their processing to selectively enhance visual stimuli most likely to be affected by positive feedback (Serences, 2008), and inhibit stimuli that are least likely to be processed further. Thus, in term of predictive coding, neural visual signals are related to internal goals and predictions based on previous input (Mumford, 1992).

Neuronal responses elicited by the second and subsequent occurrence of a stimulus are reduced compared to the first representation (Grill-Spector et al., 2006), an effect often termed “repetition suppression” (RS). Interestingly, RS has been observed within the fusiform face area (FFA) (Summerfield and Egner, 2009; Summerfield et al., 2008). In more detail, it was found that RS in the FFA reflects a relative reduction in top-down perceptual PE, when processing an expected compared with an unexpected stimulus (Summerfield and Egner, 2009; Summerfield et al., 2008). Along this line, a recent investigation revealed that activity in the FFA in response to faces and houses was indistinguishable under high face expectations and maximally differentiated under low face expectation (Egner et al., 2010). The authors explained their findings by predictive coding models. Specifically, they argued that neuronal responses in the ventral visual stream (i.e. FFA) appear to be determined by feature expectation and surprise rather than by stimulus features per se. In accordance to this finding, a previous fMRI study examined the difference between brain regions responsible for detecting the physical presence of the stimulus per se and those supporting perceptual set using a simple task that required subjects to discriminate between randomly presented images of faces, houses and cars. In the “face block” subjects had to judged whether each object was a face or not, and in the “house block” whether the object was a house or not etc. Thus, while the perceptual input was kept identical across blocks, the task encouraged subjects to employ distinct top-down perceptual sets (or templates) in the two block types, one for detecting face stimuli, and one for detecting house stimuli. Generally, faces revealed stimulus-driven activation in key regions of the face processing network, including the amygdala, IOG, FFA and vMFC. But more interestingly, compared to the activation in response to the physical stimulus (i.e. face), face block-related activity was associated with an increase in top-down connectivity from the frontal cortex to face-selective visual areas, reflected by DCM estimations. These findings suggest that subjects do indeed deploy predictive information in the service of face perception. Thus, during perceptual inference, face prediction in the vMFC are formed and back propagated via feedback connections to face-sensitive zones of the extrastriate cortex, in the service of deciding whether a stimulus is a face or not (Summerfield et al., 2006) (Figure 8). Important to note, the expectations effects on visual responses i.e. reduced visual responses with increasing number of preceding stimuli, reveal the exact opposite pattern of attention effects on visual responses, in particular that neural responses are enhanced for attended relative to unattended stimuli (Boynton, 2009; Reynolds and Heeger, 2009).

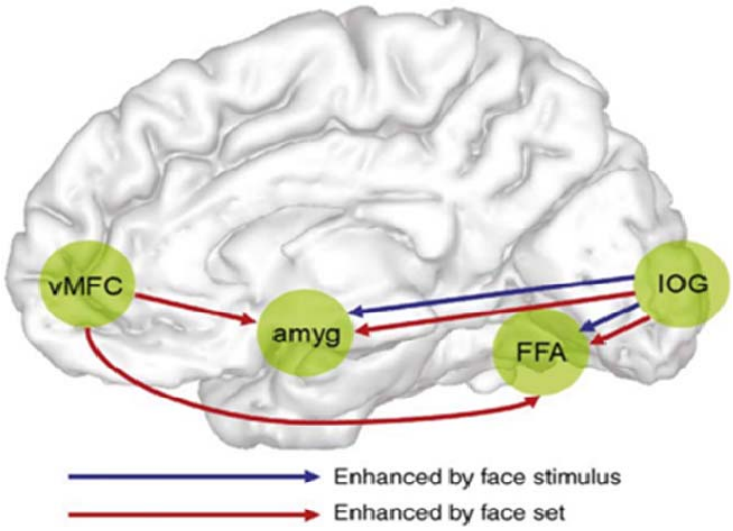

Figure 8 Dynamic causal modeling revealed that during face set blocks (as compared with house set blocks), the vMFC displayed enhanced top-down effective connectivity with the amygdala and FFA, while both face stimuli and face set affected bottom-up connectivity from the IOG to the FFA and amygdala. These data support the notion that ventral frontal regions might provide top-down perceptual "priors" to posterior regions, where these predictions are matched against incoming sensory information. Adapted from Summerfield et al. (2009).

Consistent with RS effects in the FFA, the N170 ERP shows also RS effects following repeated stimulus repetitions (Mercure et al., 2011; Vizioli et al., 2010). This is highly reasonable, given that the dipole of the N170 ERP lies in the FFA (Deffke et al., 2007). In line with this, the N170 ERP shows rapid adaptation effects (Nemrodov and Itier, 2011), which may reflect the dampening of surprise responses in error neurons to the second or subsequent presentation of a stimulus (Friston, 2005). The hierarchical structures underlying the N170 ERP in response to faces and houses has been also investigated by using DCM (David et al., 2006). Category-selectivity, as indexed by the face-selective N170, could be explained by category-specific differences in forward connections from sensory to higher areas in the ventral stream. In particular, stronger FFA and STS responses were found for faces compared to houses. This selectivity was due to an increase in coupling from IOG to FFA and from IOG to STS. This suggests that category-selectivity emerges downstream from IOG. But unfortunately, no RS effects were considered to study expectations and surprise effects in this study. Therefore, consistent to the roving MMN paradigm, parametric modulation of preceding stimulus repetitions should be considered to study visual responses more dynamically. This means that a single neuronal response to a specific object is meaningless without controlling for its temporal context. Furthermore, the effect of expectation and surprise on neural population should also be investigated as a function of stimulus valence, given that visual areas might adapt their processing to selectively enhance visual stimuli most likely to be affected by positive feedback (Serences, 2008), and inhibit stimuli that are least likely to be processed further.

Summarized, auditory (i.e. MMN) and visual (i.e. N170) neuronal responses can be explained within the framework of predictive coding models. Already early and rapid neuronal responses are influenced by top-down control, depending on the preceding context. Our brain is constantly exposed to a broad spectrum of stimuli. Predictive coding may be a general principle of the brain in which statistical relationships in the world are monitored, even when they are not attended and not direct relevant for ongoing behavior. This ensure to ignore predictable and uninteresting events in the environment, while enhancing the salience of unexpected events (den Ouden et al., 2009).

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Presentations

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Jahrespreis 2011 der Universität Zurich for excellent scientific publication: **Schmidt A, Bachmann R, Kometer M, Csomor PA, Stephan KE, Seifritz E, Vollenweider FX** (2011). Mismatch negativity encoding of prediction errors predicts S-ketamine-induced cognitive impairments. *Neuropsychopharmacology.*